# REARRANGEMENTS IN THE MONOTERPENE SERIES

A thesis presented for the
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by

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# INDEX

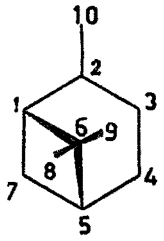
## ABSTRACT

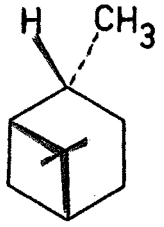
The stereochemistry of a number of (2,3)-, (2,10)- and (2,3,10)- substituted pinanes has been established. Hydroxylation of α-pinene with permanganate gave 10β-pinane-2,3α-diol, similar treatment of β-pinene gave 10β-pinane-2,10-diol. 2,10-Epoxy-10β-pinane was formed by reaction of nopinone with dimethyl sulphonium methylide. Some reactions of substituted pinanes involving carbonium ion formation at C2 have been studied. The path of rearrangement of these compounds depends on the conformation of the intermediate carbonium ion; an 'up' conformation leads to C1-C7 bond shift or rupture, whereas a 'down' conformation leads to C1-C6 bond shift or rupture. Reaction of β-pinene with mercuric acetate gave dimeric hydrocarbons. The NMR spectra of a number of pinanes have been recorded. 2,10-Epoxy-10β-pinan-3α-ol and 2,10-epoxy-10β-pinan-3β-ol reacted with aqueous alkali to give pinocarvone. The reaction was first order in epoxide and hydroxyl ion, the 3β-hydroxy-epoxide reacting faster than the 3α-hydroxy-epoxide.

# INTRODUCTION

## The Pinane Skeleton:

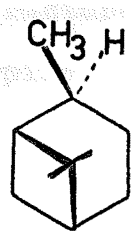
The term pinane refers to those compounds which have a 2,2,6-trimethylbicyclo-(3,1,1)-heptane skeleton, fig. 1a. It is generally assumed that the structure is drawn so that the geminal dimethyl group is closer to the reader than the C7 carbon atom. In naming substituted pinanes we designate those substituents lying below a plane containing C1,C2,C3,C4 and C5 as α and those lying above it as β. There are then two types of pinane skeletons; 10α-pinane fig. 1b and 10β-pinane fig. 1c. For an example of this naming system see fig. 1d.



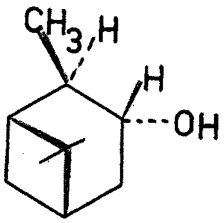




a, Pinane skeleton. b, 10α-Pinane

Fig. 1




c, 10β-Pinane




d, 10β-Pinan-3α-ol

Fig. 1

In general systematic names are used, except in those cases where the trivial name is well established. For the convenience of the reader these names have been correlated in table 1.

Table 1

| Trivial name | Systematic name |
|---|---|
| α-Pinene | Pin-2-ene |
| β-Pinene | Pin-2(10)-ene |
| trans-Pinocarveol | Pin-2(10)-en-3α-ol |
| cis-Pinocarveol | Pin-2(10)-en-3β-ol |
| Pinocarvone | Pin-2(10)-en-3-one |
| Nopinone | 6,6-Dimethyl-norpinan-2-one |
| Apobornane | 7,7-Dimethyl-norbornane |

The (3,1,1)-bicycloheptane structure was first postulated by Wagner[1], who correctly assigned the structure of α-pinene (1). A partial synthesis of α-pinene was achieved by Ruzicka and Trebler[2], who prepared α-pinene from (DL)-pinonic acid (2). Pinonic acid was later synthesised by Rao[3] completing the total synthesis of α-pinene.

Recent X-ray analyses on 2,4α-dibromo-10β-pinan-3-one[4] (3), 2,10-dibromo-10β-pinan-3-one[5] (4), 3β-bromonopinone (5) and 3β-chloronopinone (6)[6] support the (3,1,1)-bicycloheptane structure and give additional information about the stereochemistry of pinanes. Contrary to the suggestion of Bhatt[7], the four membered ring is puckered. The degree of 'buckling' of the four membered ring is indicated by the angle θ in fig. 2a. This angle has been found to be between 35 and 40° for pinanes[5], which is considerably more than the 20 degrees found for cyclobutane[8]. The internal angles of the four membered ring are found to be ca. 88° [4,6]. Jameson[7] quotes values of 82 and 93° for internal angles at C6 or C7 and C1 or C5, but since the molecule concerned, 2,10-dibromo-10β-pinan-3-one (4), is heavily substituted this is probably exceptional.

The pinanes can exist in two distinct conformations, e.g. as the 'up' conformer fig. 2b or the 'down' conformer fig. 2c.

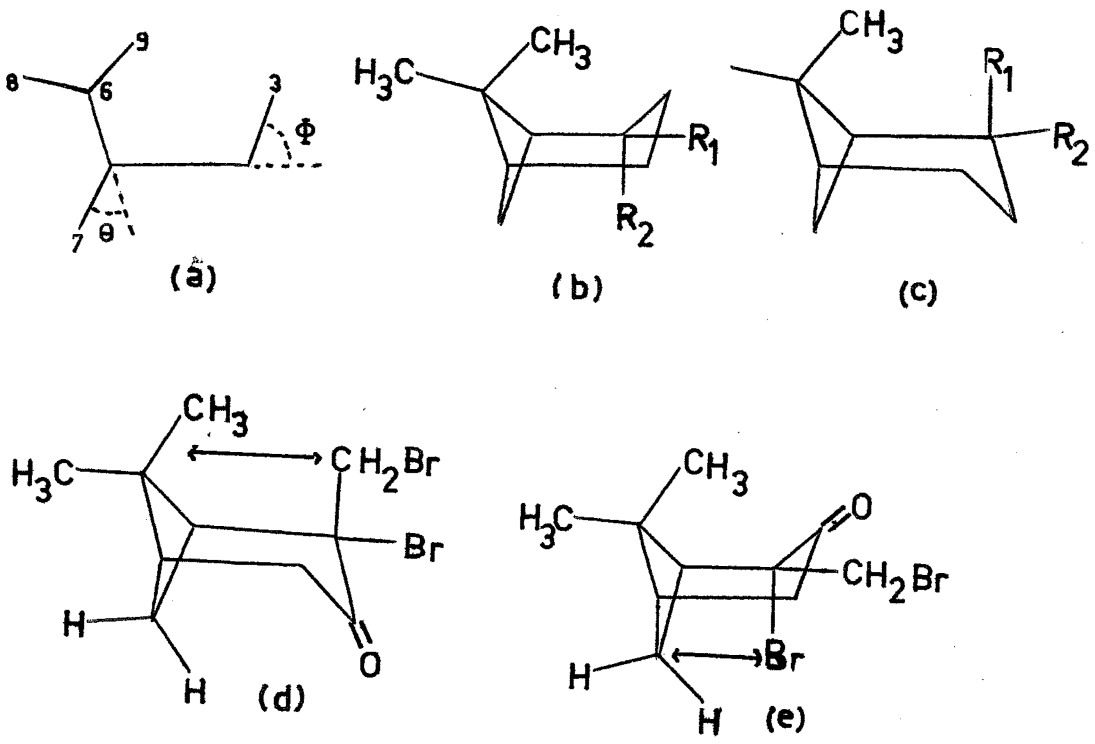



Fig. 2

The conformation is defined by the angle Φ that the plane containing C2, C3 and C4 makes with the plane containing C1,C2,C4 and C5, fig. 2a. The angle is made negative for a 'down' conformation and positive for an 'up' conformation. The results obtained from the four X-ray analyses above is listed in table 2.

Table 2

| Compound | | Angle $\Phi^{o}$ |
|---|---|---|
| 2,10-dibromo-10β-pinan-3-one | (4) | average- + 10. |
| 2,4-dibromo-10β-pinan-3-one | (3) | + 6.7 |
| 3β-bromonopinone | (5) | - 29.9 |
| 3β-chloronopinone | (6) | - 30.6 |

The values can be rationalised in terms of the adoption of that conformation in which non-bonded interactions are minimised. For example in the case of 2,10-dibromo-10β-pinan-3-one the large bromine groups determine the conformation. In a 'down' conformation, fig. 2d, the interaction of the axial C10 $CH_2$-Br group with the geminal dimethyl group would be great; whereas in an 'up' conformation, fig. 2e, the interaction of the axial 2α-bromine with the C7 methylene group is prohibitive. The result is a compromise near-planar conformation ($\Phi = 10^{\circ}$) allowing both large groups to attain a semi-equatorial configuration. These results do not, however, provide information about simple pinanes, since they refer to compounds that are heavily substituted and contain an $sp_2$ centre, in the form of a carbonyl group, in the ring.

An attempt has been made by Biemann[9] to assign the conformation of the pinan-2-ols on the basis of their mass spectrum. It was suggested that the stability of the ion $M^+$ is inversely dependent on the amount of steric interaction in the molecule.

The ratio of $M^+$ to total ion formation, a measure of the stability of $M^+$, was smaller for 10α-pinan-2-ol (7) than for the epimer (8). Greater steric interference in the 10α-epimer is only consistent with both

being in the 'up' conformation, assuming that a methyl group is bigger than an OH group. Since the two compounds are epimeric their interactions, in the same conformer, differ only because of the different size of the methyl and OH groups. In the 'up' conformation 10α-pinan-2-ol has an axial methyl - alkyl interaction, fig. 3a; whereas 10β-pinan-2-ol (8) has an axial hydroxyl - alkyl interaction, fig. 3b. In the 'down' conformation 10α-pinan-2-ol has a hydroxyl - gem. dimethyl interaction, fig. 3c, and 10β-pinan-2-ol a methyl - gem. dimethyl interaction, fig. 3d.

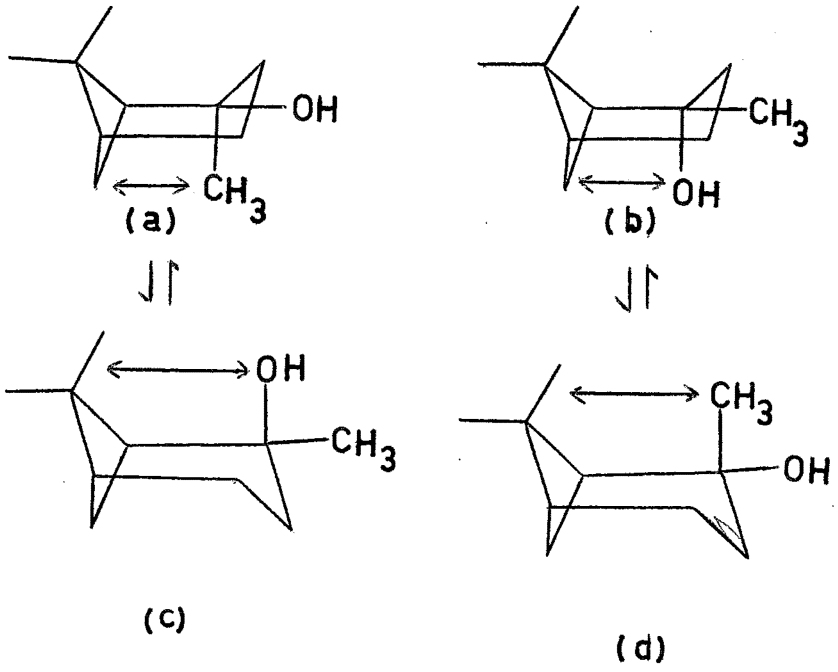



Fig. 3

The results apply only to the gas phase; in the liquid phase solvation is likely to increase the effective size of the hydroxyl group. Since most of the chemistry of pinanes is carried out in the liquid phase, it is important to be able to assign the conformation in this phase.

The pinan-2-ols have been assigned[10] the 'down' conformation, fig. 3c and d, on the basis of their reactivity with acetic anhydride. Similarly solvolysis of the supposed 6,6-dimethylnorpinan-2-ols[11] (9 and 10) has led to the assignment of the 'down' conformation for these two alcohols. These results were later shown[12] to be erroneous, since the compounds concerned were not in fact (3,1,1)-, but (2,2,1)-bicycloheptanes. However, since the main object of studying the conformation of pinanes in solution is to relate the conformation to the reactivity and path of reaction, an independent physical method is required in order to avoid circular reasoning.

This method is provided by NMR spectroscopy, but sufficient data is not yet available. A number of assignments of conformation have been made on the basis of chemical shifts[13,14,15,16]. Ideally these assignments of conformation should be based on spin-spin coupling constants of protons at C2, C3 and C4. Unfortunately these coupling constants cannot normally

be readily determined, due to the complexity of the spectra. The exact relationship between the dihedral angle ($\Phi$) and the coupling constant (J) is not known; but use has been made of the relationship in eq. 1, derived by Karplus[17] for substituted ethanes.

$$J = 4.22 - 0.5\cos\Phi + 4.5\cos 2\Phi \qquad \text{Eq. 1}$$

Stereochemical Aspects

Although the stereochemistry of the substituted pinanes has been largely established by Schmidt[18], there are still areas of doubt.

Schmidt's assignments were based mainly on the von Auwers-Skita rule[19,20,21], which does not necessarily apply to this system. The configuration of the pinan-3-ols (11,12,13 and 14) was disputed by Bose[22], who reassigned the configuration at C3 on the basis of a conformational analysis, and Huckel[23] who based his assignment on the fast rate of hydrolysis of isopinocampheyl tosylate (15). The rapid rate of hydrolysis was taken as an indication of a cis relationship between the tosyloxy and C10 methyl groups. This assignment was shown to be invalid[16] since the methane sulphonate ester of neoisopinocampheol (14) hydrolysed three times as fast as the sulphonate of the epimeric isopinocampheol (12).

An example of the use of the mechanism of formation as proof of structure was provided by Zweifel and Brown[16] who confirmed the original assignments of Schmidt[24] by the formation of 10β-pinan-3α-ol (12), identical to Schmidt's isopinocampheol, by the hydroboration of α-pinene. The basis of this proof is the preferred attack on the less hindered α-face of the double bond.

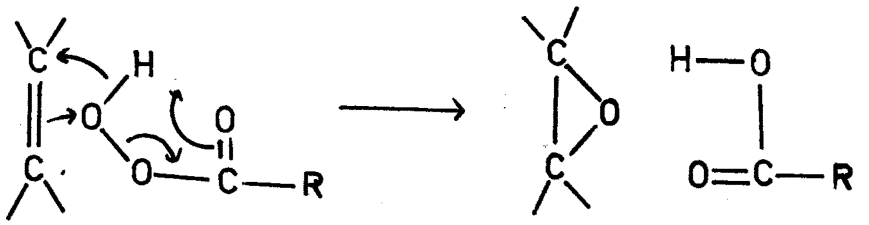
An illustration of preferred attack on the α-face is provided by the reaction of diimide with α- and β-pinene[25] (16). α-Pinene gave a 99:1 and β-pinene a 96:4 ratio of 10β-pinane (17) to 10α-pinane (18). A similar result was obtained by hydroboronation of β-pinene followed by 'acidolysis'[16] with propionic acid.

The epoxidation of α-pinene[26] with peracid gives essentially pure 2,3α-epoxy-10β-pinane (19), since the reaction of this epoxide with lithium diethylamide[27] gives trans-pinocarveol (20) in 92% yield.

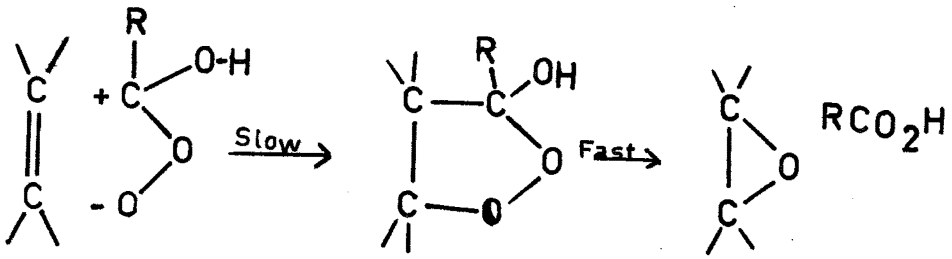
Epoxidation of β-pinene with perbenzoic acid has been reported[28,29] to give an 80:20 mixture of 2,10-epoxy-10β-pinane (21) and 2,10-epoxy-10α-pinane (22) based on the relative amounts of epimeric alcohols (7 and 8) formed by reduction of this epoxide mixture with lithium aluminium hydride. The method of estimating the ratio of products was however

only at best semi-quantitative. A previous paper[30] did not report any epimers from this reaction.

The validity of the molecular mechanism proposed by Bartlett[31], fig. 4a, for the peracid epoxidation of olefins is currently in doubt. Kwart and Hoffman[32] have proposed a 1,3-dipolar addition, fig. 4b, as the rate determining step. This mechanism is however not supported by a recent rate analysis[33], although the evidence may not be conclusive[34].




(a)




(b)

Fig. 4

Peracid epoxidation is generally considered to be stereospecific[35] and stereoselective[36]. The indication that the epoxidation of β-pinene is less stereoselective than epoxidation of α-pinene is consistent with an electrophilic[37] attack on the C2-C10 bond, since steric interference will be less at the C10 atom than at the C2 or C3 atom.

The epoxidation of pinocarvone (23) with alkaline hydrogen peroxide has been reported[38] to give a 1:1 ratio of epimers. This reaction is not stereospecific[39]. It probably involves an initial attack by the hydroperoxide ion on the C10 atom followed by elimination of hydroxyl ion. The original reaction scheme[40], fig. 4, is supported by recent work[41].

The lack of stereospecificity in this reaction is thought to be due to the possibility of rotation about the C1 - C2 bond. Similarly rotation about the C2 - C10 bond, in the intermediate from pinocarvone, gives a mixture of epimers. In the intermediate formed by epoxidation of pin-2-en-10-ol (24) no such rotation is possible due to the constraint of the ring system and only one product, 2,3α-epoxy-pinan-10-ol (60), is formed[38].

Hydroxylation of α-pinene with aqueous permanganate has been reported[42] to give a diol, m.p. 56° and a ketol of unknown configuration.

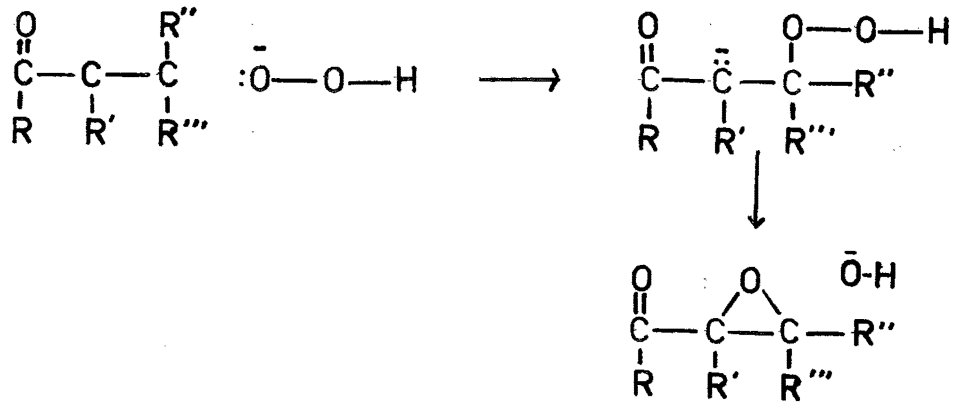


Fig. 5

The ketol was later reduced with sodium[43] to give 10β-pinan-3α-ol (12). Reduction of the ketol with hydrogen over a nickel-platinum catalyst gave a diol[44], m.p. 156 - 160°.

Schmidt[45] reduced the ketol with aluminium isopropoxide, to give a diol, m.p. 56°, and with lithium aluminium hydride to give a diol, m.p. 156°. These diols were shown to be 10β-pinane-2,3α-diol (27) and 10β-pinane-2,3β-diol (26) respectively by use of the von Auwers-Skita rule and the rapid rate of oxidation of the first diol, m.p. 56°, with lead tetraacetate, indicating a cis diol.

These assignments are in full accord with the expected mode of reaction. The hydroxylation of an alkene involves a cyclic transition state[47] similar to that observed for hydroxylation by osmium tetra-oxide[48]. The over-all result is the cis addition of

two hydroxyl groups on the least hindered side of the molecule.

The reduction of the ketol (25) with lithium aluminium hydride is consistent with the expected α-face attack of a hydride ion to give the 3β-diol (26).

In a later paper[46] Schmidt reacted the diols (27) and (26) with dilute sulphuric acid and obtained fenchane-2α,6β-diol (28) and pinol (29) respectively. On the basis of this work Schmidt reassigned the configuration of C2, without changes in C3 stereochemistry, such that the stereochemistry for a concerted rearrangement to the fenchane skeleton, fig. 6, was present in diol (27).

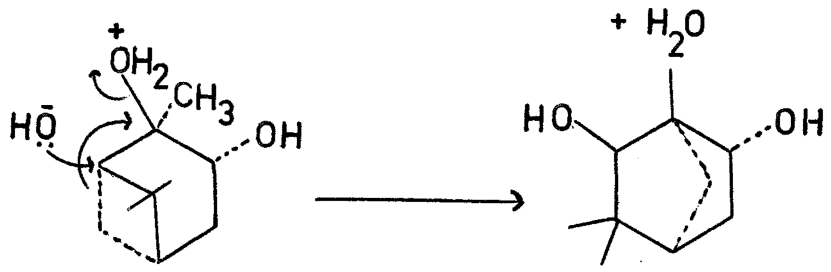



Fig. 6

This method of determining the configuration of C2 had previously been used successfully by Burrows and Eastman[10] to establish the structure of the pinan-2-ols. Reaction of 10α-pinan-2-ol with acetic

anhydride gave mainly fenchyl acetate (30), while reaction of the epimeric alcohol, 10β-pinan-2-ol (8), gave mainly terpinyl acetate (31) and bornyl acetate (32).

Similarly the reaction of 10α-pinan-2-ol (7) with hydrogen chloride gave mainly fenchyl chloride (33), while the epimeric alcohol gave bornyl (34) and fenchyl chloride[28].

However for the diol, m.p. 56°, derived from α-pinene difficulties arise when the rearrangement in acid to the fenchane diol (28) is regarded as a concerted process, requiring as it would a fixed relative stereochemistry of the C7-C1 bond and the C2-OH bond. The assignment of a structure with a 2β OH group, fig. 6, to diol m.p. 56° requires the permanganate oxidation to be trans (for 3α-OH), or to give solely the product corresponding to cis-attack on the hindered β-face (for 3β-OH).

Hydroxylation of β-pinene with dilute aqueous permanganate has been reported[49,50] to give a pinane-2,10-diol, the configuration at C2 was not determined. Further oxidation gave norpinic acid (61) and finally nopinone (62).

Hydroxylation of β-pinene with osmium tetroxide - hydrogen peroxide in ether has been reported[51] to give a mixture of epimeric diols, m.p. 55°.

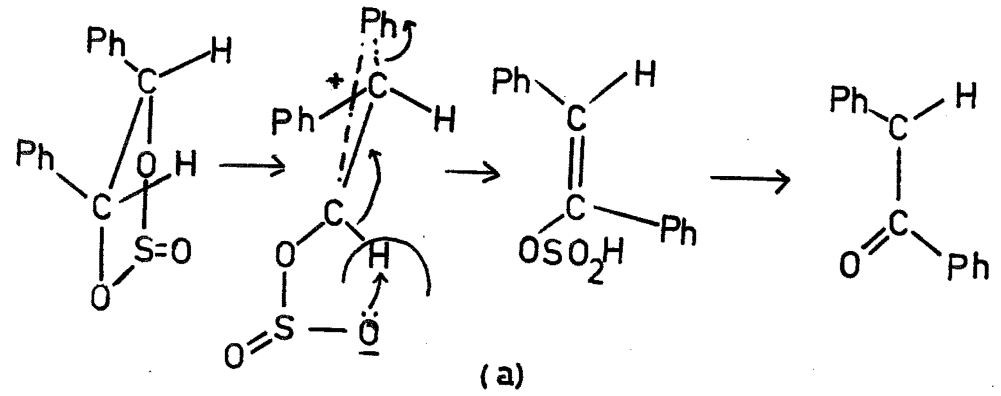
Ring Opening Reactions of Epoxides, Cyclic Sulphites and Cyclic Carbonates:

The acid catalysed reactions of epoxides have received extensive attention. In particular the opening of steroid epoxides with boron trifluoride etherate has been the subject of much work[52].

From an analysis of ketonic products of epoxide opening Hartshorn and Kirk have made the postulate that "axial cleavage of an epoxide presents a reaction pathway of lower energy than equatorial cleavage, unless special structural features are present which specifically oppose the axial mode of cleavage of a particular epoxide". For the epoxides in this thesis there is no question of the direction of epoxide opening since there is only one tertiary centre; but the preferred conformation of the transition state may determine the products.

The thermal rearrangement of cyclic sulphites is of interest here, since they may involve the formation of a carbonium ion. Denivelle[53] has found that the thermal rearrangement of butane-2,3-diol cyclic sulphite gives the 2,3-epoxide and ethyl methyl ketone. Price and Berti[54] have studied the thermal rearrangement of the cyclic sulphites from meso- and (DL)-hydro benzoin. The cis- sulphite, fig. 7a, (from the meso-

diol) gives desoxybenzoin, whereas the trans-sulphite, fig. 7b, gives diphenyl-acetaldehyde. The mechanism is explained on the basis of a bridged ion intermediate. The abstraction of a proton by the sulphinate group leads to the products above.



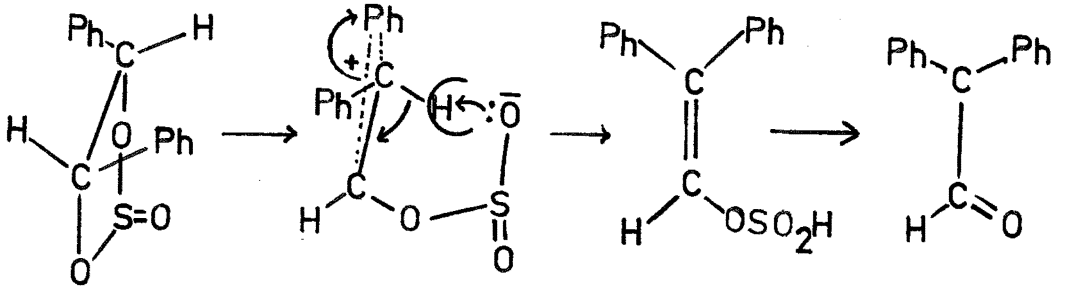



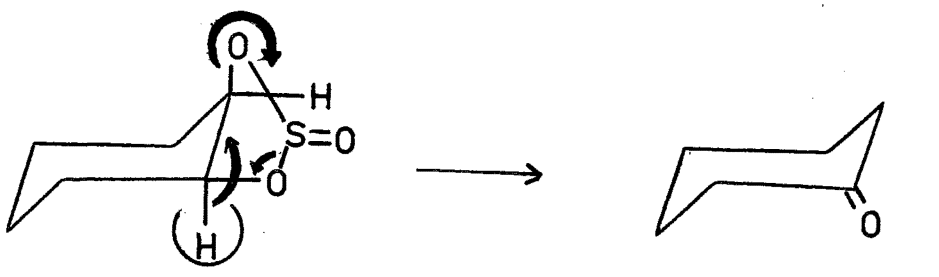

Fig. 7

It is assumed that abstraction of a cis-β-proton is favoured over abstraction of an α-proton, since the intermediate in the former case involves a quasi-six-membered ring, whereas in the latter case a five membered ring is involved.

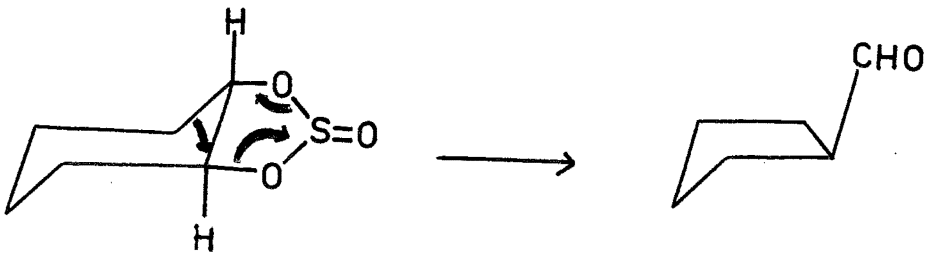
The cyclic sulphites of cyclohexane cis- and trans-diol gave cyclohexanone and cyclopentane aldehyde respectively under the same conditions.

These reactions are explained in terms of opening of the ring concerted with a hydride or alkyl shift. In the case of the cis- isomer, fig. 8a, a hydride shift is favoured since the -H atom is trans to and coplanar with the axial C-O bond.

In the trans-isomer, fig. 8b, breaking of either C-O bond will result in an alkyl shift. The mechanisms outlined by Price and Berti are illustrated in fig. 8.




(a)




(b)

Fig. 8

Cyclic sulphites are usually formed by the reaction of thionyl chloride on the diol[53]. It is interesting to note that they are also formed by the reaction of sulphur dioxide on an epoxide[55]. Presumably this reaction involves acid opening of the epoxide followed by ring closure, fig. 9. Since epoxides have been formed from a cyclic sulphite[53], this reaction is probably reversible.

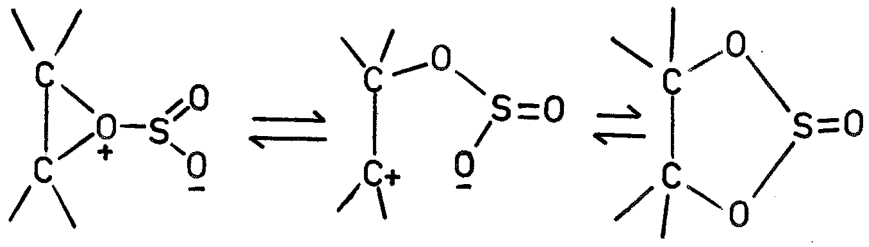


Fig. 9

The cyclic carbonates, formed by the reaction of phosgene[56], ethyl chloroformate[57] or diethylcarbonate[58] on a diol or the reaction of an epoxide with carbon monoxide[59], are similar in structure to the cyclic sulphites, but react differently on heating. In general they give rise to cyclic ethers[58,60,61], allyl alcohols[58] or in one instance an aldehyde[58].

These reactions, which are base catalysed, are considered[58] to proceed via an alkoxide intermediate

rather than a carbonium ion. The mechanism outlined by Searles and Hummel[58] for the formation of an ether or aldehyde is shown in fig. 10.

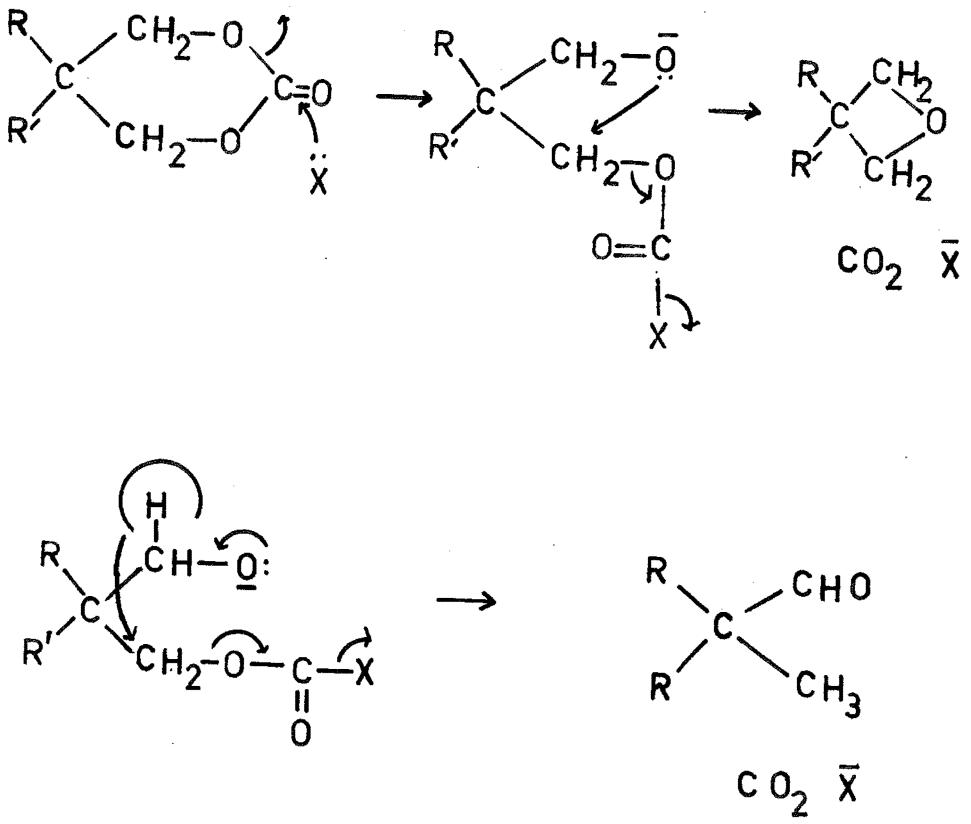


Fig. 10

Reactions Involving Carbonium Ion Formation at the C2 Position:

A large number of reactions involving some degree of carbonium ion formation at C2 have been studied. In general they lead to skeletal rearrangements involving a 1,2 alkyl shift or rupture of the C1-C6

bond.

The skeletal transformations observed are outlined in fig. 11.

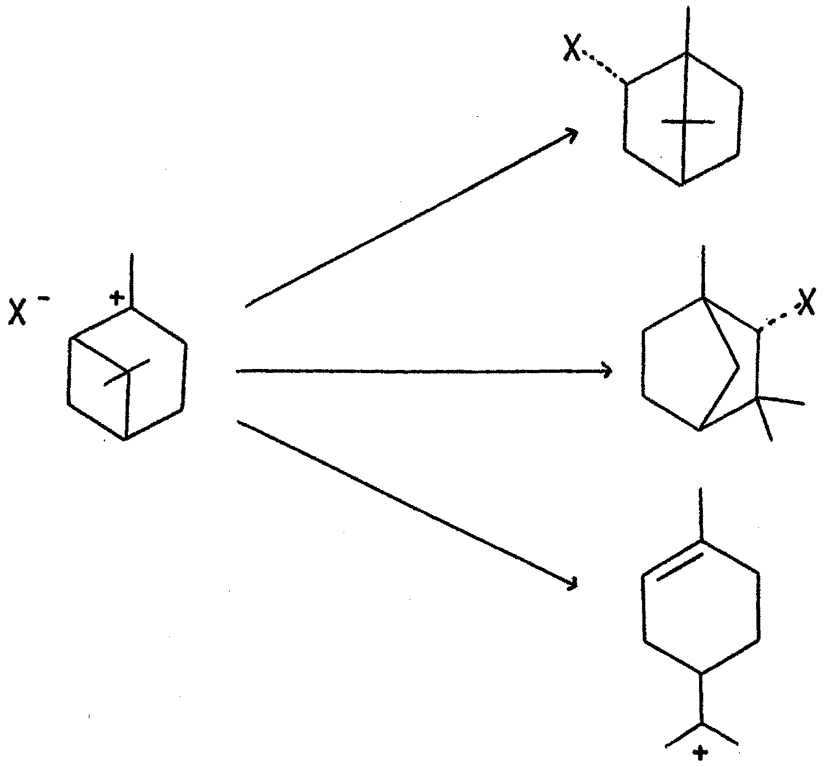



Fig. 11

The generation of C2-carbonium ions by treatment of α- and β-pinene with acid have been extensively studied. The reaction of α-pinene with anhydrous hydrogen chloride at room temperature gives rise mainly to bornyl chloride[62] (34), while reaction at -70° in ether gives the 2-chloropinane (35), which rearranges at room temperature to give bornyl chloride. The

rate is extremely sensitive to solvent interactions being 500 times faster in chlorobenzene than in petroleum ether[63].

Reaction of α-pinene with dilute sulphuric acid gives mainly α-terpineol (36). A recent quantitative study[64] reports the following ratio of products at t = 0 (by extrapolation); α-terpineol 62%, borneol (37) 3%, fenchyl alcohol (38) 3%, limonene (39) 14% and terpinolene (40) 11%. Similar results were obtained using perchloric acid. The reactions of β-pinene (16) with acids have not been investigated as fully as those of α-pinene, though it appears[65] that the products are at least qualitatively the same.

The reaction of the pinan-2-ols with acetic anhydride gave monoacetates and hydrocarbons, table 3.

Table 3

| Compound | Reaction Product (%) | | | |
|---|---|---|---|---|
| | Bornyl Acetate | Fenchyl Acetate | Terpinyl Acetate | Hydro-Carbons |
| 10α-pinan-2-ol | - | 40-50 | 5-10 | 40-50 |
| 10β-pinan-2-ol | 5 | - | 40-60 | 30-50 |

Similarly the reaction of 10α-pinan-2-ol (7) with hydrogen chloride gives mainly fenchyl chloride[29] (33). The reaction of 10β-pinan-2-ol under the same conditions, however, gives both bornyl and fenchyl chloride.

Reaction of both isomers with hydrogen fluoride gives only 8-fluoro-Δ'-p-methene[29] (41).

Solvolysis of the p-nitrobenzoates of 10α-pinan-2-ol and 10β-pinan-2-ol in aqueous acetone gives β- and α-pinene respectively[66].

These rearrangements have been reviewed by Banthorpe and Whittaker[67], who have rationalised the reaction of the pinan-2-ols with acetic anhydride in terms of the intermediate non-classical carbonium ions in fig. 12.

In view of the present controversy over the use of bridged carbonium ions[68,69], it seems pertinent to assess the evidence for the non-classical carbonium ions 12b and 12f. It should be pointed out here that these intermediates were not postulated in the original work by Eastman and Burrows[10].

Banthorpe and Whittaker have postulated the bridged carbonium ions fig. 12b and 12f as the intermediates in reaction of 10α-pinan-2-ol, fig. 12a, and 10β-pinan-2-ol, fig.12e, respectively.

For the formation of terpinyl acetate the

carbonium ion 12f can collapse to give the discrete ion 11d followed by reaction with the solvent to give the product, 12d.

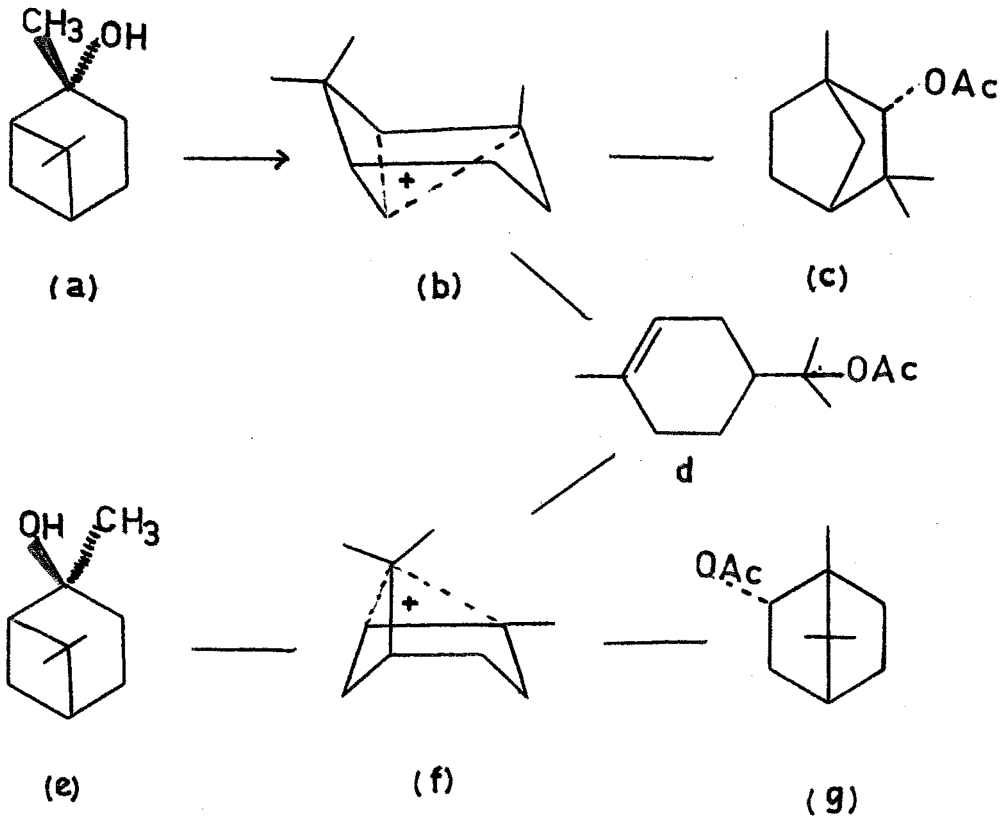



Fig. 12

The product obtained is, however, also consistent with a concerted removal of the hydroxyl group and collapse of the C1-C6 bond, or collapse of the classical carbonium ion 11a.

There is no similar process by which the carbonium ion 12b can collapse and react with the

solvent to produce terpinyl acetate. The proposal of the carbonium ion 12f as an intermediate in the formation of terpinyl acetate is unnecessary, the proposal of the carbonium ion 12b is both unnecessary and misleading.

The formation of the endo-acetates is consistent not only with the involvement of non-classical ions 12b and 12f, but also with a degree of concertion in the attack by nucleophile at C1 with the rearrangement of ion 11a by C6 or C7 migration.

Since attack on a discrete classical bornyl ion should give the exo product this ion is not involved.

In a recent publication[70] Salmon and Whittaker described the solvolysis of the pinan-10-ol tosylates in methanol containing an equimolar quantity of methoxide. The reaction involves the formation of a carbonium ion a C10, which will rearrange to give a carbonium ion at C2. On the basis of the formation of 2% bornyl methyl ether, fig. 13b, containing less than 1% of the epimeric isobornyl ether, it was argued that a carbonium ion of the type 12f was the intermediate since a discrete bornyl ion would give the exo product, isobornyl ether. The authors apparently disregarded the possibility of some degree of concertion of attack by entering nucleophile with the rearrangement of the carbon skeleton, fig. 13.

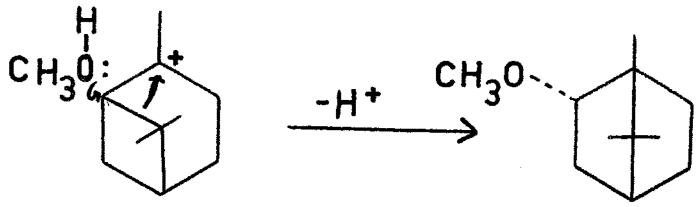



Fig. 13

It is pertinent to note here that reactions leading to the formation of a carbonium ion at C2 give bornyl or fenchyl derivatives in the presence of a nucleophile[62,10,28], when no nucleophile is present menthenes are obtained[29,64]. In view of this observation it seems pertinent to attempt to discuss the gross energy changes associated with the carbonium ion reaction pinane → bornane. Some indication of the relative energies of the two systems may be obtained from the reported combustion data for pinanes and bornanes.

From a recent combustion study[71] a difference of ca. 2 kcal/mole was found for the heat of combustion of α- and β-pinene, β-pinene having the larger value. From some previous work it was found that the heat of combustion of α-pinene is ca. 2kcal/mole greater than the value for camphene[72] (42). Together these results indicate a decrease of ca. 4kcal/mole in going from β-pinene to camphene. To

a first approximation we may say then that the release in strain in going from a (3,1,1)- to a (2,2,1)-bicycloheptane system is in the order of 4 kcal/mole. This would not be sufficient to offset the effect of the increase in energy of going from a tertiary to a secondary carbonium ion, which has been quoted at 6.6 kcal/mole[68]. The p-menthenyl carbonium ion, fig. 11d, is certainly more stable than either bornyl or pinyl ions since it is not strained (the difference in strain energy between a pinene and a methane is thought[73] to be 11 kcal/mole,) and is a tertiary carbonium ion.

If these values are a true representation of the energy changes involved, it is not surprising that the reactions of pinanes to give bornanes or fenchanes should involve a concerted attack by the solvent or of a nucleophile. In the absence of a nucleophile the pinyl ion, 11a, will collapse to give the much more stable anion, 11d.

The results of Salmon and Whittaker[70] indicate that 38% of the product is derived from the carbonium ion, 11d, and 26% from the ion, 11a. Only 2% of the product has a bornane skeleton.

Whereas there is no sign of anchimeric assistance in the solvolysis of the pinan-2-ol p-nitrobenzoates[66], the 6,6-dimethylnorpinane-2β-brosylate (43)

solvolyses $10^5$ times faster than apobornyl brosylate[74] (44). In this reaction the exo substituted product is obtained. This is consistent with the formations of a non-classical apobornyl ion (45) or with a classical apobornyl ion (46) taking into account the torsional effects predicted by Schleyer[75].

Since the transition from a 6,6-dimethylnorpinyl ion to the apobornyl ion does not involve a decrease in the substitution of the carbonium ion it is more favoured than the corresponding pinyl to bornyl ion transition. It is therefore not surprising that in this case products, corresponding to a discrete apobornyl ion, are found.

A number of rearrangements of 3 and 10-substituted pinanes have also been studied. 2,3-Epoxy-10β-pinane (19) reacts with 'Lewis' acids to give 2,2,3-trimethylcyclopent-3-en-1-acetaldehyde[76,77] (47) and 10α-pinan-3-one[78] (48). The formation of ketone (48) by reaction with zinc bromide is disputed in a recent paper[79]. Reactions with protic acids give, in addition to these products, substituted menthenes and <u>trans</u>-pinocarveol[76] (20).

2,10-Epoxy-10β-pinane (21) reacts with anhydrous zinc halides to give pinan-10-al [74] of undefined stereochemistry. Reaction with alumina gave

10α-pinan-10-al (49) and pin-2-en-10-ol (50). Prolonged reaction gave menth-1-en-7-al[80] (51). The epoxide (21) reacted with acetic anhydride and acetic acid to give 10β-pinan-10-al (52) and p-menth-1-en-7-al. Reaction with acetic or formic acid gave the corresponding 8-monoesters of menth-1-ene-7,8-diol (53a and b). Since the yield of aldehyde is generally low, the difference in stereochemistry of the products formed may be due to the removal of one or other of the aldehydes by further reaction. For example, 10α-pinan-10-al has been found to react with acetic acid - acetic anhydride to give a diacetate[81].

trans-Pinocarveol (20) reacted with dilute sulphuric acid to give the fenchane diol[46] (28). Reaction with hydrogen bromide gave the corresponding bromofenchol[82] (54). Bromination gave the dibromofenchol and an aldehyde[83]. cis-Pinocarveol (56) reacted with dilute sulphuric acid to give pinol[46] (29), reaction with hydrogen bromide gave the bromoborneol[84] (57).

10β-Pinane-2,3α-diol (27) and 10β-pinane-2,3β-diol (26) gave the same products as trans- and cis-pinocarveol respectively with dilute sulphuric acid.

From an examination of these results it appears that the 3-hydroxyl group is consistently governing

the path of rearrangement.

Compounds with a 3α-hydroxyl group give rise to fenchanes, whereas compounds with a 3β hydroxyl group give compounds derived by a C6 shift, i.e. bornanes or pinol. In view of the consistency of this effect there appears to be no justification for assigning the stereochemistry at C2, on the basis of the reaction path, in this system.

The effect of the 3-hydroxyl group is rationalised in the discussion.

Preparation of substituted pinanes

The numerous skeletal rearrangements that pinanes undergo provide an interesting area for study. However, at the same time, the facility with which these compounds undergo rearrangement provides the main barrier to the synthesis of substituted pinanes. α- and β-pinene are readily available from commercial sources and provide suitable starting materials. Only routes which do not involve a carbonium ion at C2 will result in a product with a pinane skeleton. A number of synthetic methods are quite successful, in particular hydroboration, reduction and epoxidation which have already been discussed. The preparation of pinanes has recently been reviewed[85].

The syntheses of pinocarvone and the pinocarveols are of great importance to the work in this thesis.

Pinocarvone (23) has been synthesised from α-pinene through its nitroso-chloride[86] (58). On treatment with base this compound eliminates to give the oxime of pinocarvone, which can be hydrolysed to the ketone with oxalic acid. This method can only be used to prepare (DL) pinocarvone, since the nitroso-chloride is a dimeric meso form. Yields are low.

Pinocarvone has also been prepared by oxidation of β-pinene with selenium dioxide, although the product was initially assumed[87] to be pin-1-en-3-one (59). This method of synthesis has more recently been utilised to give pinocarvone in ca. 30% yield[84,88]. Oxidation of trans-pinocarveol with chromium trioxide gives only a poor yield of pinocarvone[89].

cis-Pinocarveol (56) can be produced in good yield from pinocarvone by Meerwein-Ponndorf-Verley reduction or by bromination followed by debromination reduction with zinc and acetic acid[90].

trans-Pinocarveol (20) can be prepared by oxidation of β-pinene with lead-tetraacetate followed by alkaline hydrolysis[84,91]. It has also been prepared by the reaction of selenium dioxide on β-pinene[92,93] and by the reaction of molecular oxygen and ultraviolet light on α-pinene[94].

In a recent review by Banthorpe and Whittaker[85] it was stated that 'all these reactions give yields of 70% or greater', however, on examination of the papers referred to the yields were found to be 32, 53 - 62 and 35% respectively'.

In the past, investigations in the pinane series have been thwarted by a number of problems, mainly arising from the complex reaction mixtures obtained. The recent development of gas-liquid chromatography has provided a means of analysing the mixtures and pure samples can be obtained by preparative chromatography.

The use of NMR spectroscopy provides a powerful analytical tool. Often the structure of a compound can be determined from its NMR spectrum alone. (The application of NMR spectroscopy is discussed later in this thesis.)

The main aim of this thesis has been to elucidate the reactions involving a carbonium ion at position C2 of the pinane skeleton.

# DISCUSSION

## Chapter 1

## THE PREPARATION AND STEREOCHEMISTRY OF (2,3)-, (2,10)-, AND (2,3,10)-OXYGENATED PINANES

As was pointed out in the introduction the stereochemistry of the pinane diols is uncertain. For the work in this thesis it was necessary to prove their configuration rigorously. The proof of the stereochemistry of these diols and hence a number of associated compounds is outlined in these sections.

### Section 1 2,10 oxygenated pinanes

Epoxidation of pure β-pinene with perbenzoic acid under the conditions described in the literature[27] gave 2,10-epoxy-material in 66% yield. Comparison of the NMR spectrum of this epoxide material with the NMR spectrum of 2,10-epoxy-10α-pinane (22), discussed later, showed the epoxide to contain no more than 8% of the 10α-pinane epoxide contrary to the suggestions of previous workers[27,28]. Reduction of the epoxide with lithium aluminium hydride gave 10β-pinan-2-ol (8) in 91% yield. The alcohol was shown to contain less than 0.5% of the epimer (by g.l.c.).

Hydroxylation of β-pinene with dilute aqueous

permanganate solution gave 10β-pinane-2,10-diol (63) m.p. 75° [48,49] in low yield. Purification by recrystallisation from pentane gave material m.p. 83.5°. Hydroxylation with osmium tetroxide - hydrogen peroxide in anhydrous ether under the conditions of Dupont and Dulou gave a diol m.p. 82° which was shown by NMR and IR to be identical with the sample produced by permanganate oxidation. Contrary to the suggestion of Dupont and Dulou no trace of the epimeric diol, 10α-pinane-2,10-diol (64) could be detected in the NMR spectrum.

Reaction of 10β-pinane-2,10-diol (63) with p-toluenesulphonic acid in pyridine gave a gum, which was assigned the structure (65), 10-tosyloxy-10β-pinan-2-ol, on the basis of its NMR spectrum which exhibited signals of 3.83 ppm (2H singlet; C10 protons), 1.17 and 0.77 ppm (3H each; C8 and C9 methyl groups) and 2.44 ppm (4H; p-methyl group and 2α-OH); treatment of the sample with deuterium oxide reduced the integral of the 2.44 ppm signal to 3 protons (p-methyl group) thus confirming the assumed superposition of signals. Reduction of 10-tosyloxy-10β-pinan-2-ol with lithium aluminium hydride gave 10β-pinan-2-ol (8), identical with the sample produced by reduction of the epoxide (21) by NMR and IR, thus proving the configuration of the 2,10 diol to be

10β-pinane-2,10-diol.

β-Pinene was oxidised by ozone at -70° to give nopinone (62) (6,6-dimethylnorpin-2-one) in good yield. This ketone reacted with methylmagnesium iodide to give 10α-pinan-2-ol (7). No epimeric alcohol impurity could be demonstrated by g.l.c. ( < 0.5%). Reaction of nopinone with dimethyl sulphonium methylide afforded 2,10-epoxy-10α-pinane (22), which has not previously been prepared. The compound was a liquid, m.p. - 18.5°, yield - 84%. The NMR and IR spectrum and microanalysis were consistent with the structure assigned.

Reduction of the epoxide (22) with lithium aluminium hydride gave 10α-pinan-2-ol (7; 63%) identical with the sample obtained by MeMgBr on nopinone thus proving the configuration of the epoxide. The stereochemistry of the products derived by hydroxylation or epoxidation of β-pinene are consistent with considerable steric hindrance to attack on the β-face. Similarly the reactions of nopinone (62) with methyl Grignard and dimethyl sulphonium methylide are in accord with hindrance to the β-face. It is assumed that the mechanism, proposed by Hruby and Williams (fig. 14), applies.

It is pertinent to note here that these last two reactions involve a nucleophilic attack of C2, whereas

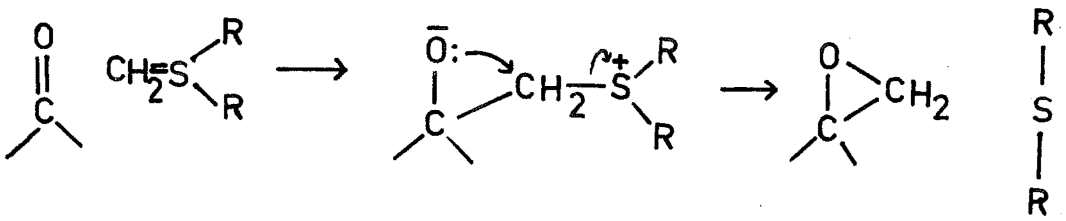


Fig. 14

peracid epoxidation involves an electrophilic attack at the C2-C10 bond. This explains the greater stereoselectivity of the ketone reactions, since the steric effect of the geminal dimethyl group would be more pronounced at the C2 position than at the C2-C10 bond.

Two cyclic ester derivatives of 10β-pinane-2,10-diol (63) were prepared. Reaction of the diol with thionyl chloride in pyridine gave 10β-pinane-2,10-diol cyclic sulphite (66) as a crystalline solid m.p. 80°. The analysis and IR spectrum were consistent with the structure assigned. The NMR spectrum exhibited signals of 1.31 ppm (3H; C8 methyl protons), 0.89 ppm (3H; C9 methyl protons) and 4.28 ppm (2H, quartet, $J_{AB}$ = 9 cps, $\Delta\nu$ = 0.10 ppm). 10β-Pinane-2,10-diol (63) reacted with diethyl carbonate to give 10β-pinane-2,10-diol cyclic carbonate (67) as a crystalline solid, m.p. 142°. The microanalysis and a band at 1795 $cm^{-1}$ in the IR spectrum were consistent with the structure assigned. The NMR spectrum exhibited signals at

1.26 (3H; C8 methyl protons), 0.83 (3H; C9 methyl protons) and 4.12 ppm (2H; C10 protons.

The stereochemistry at position C2 in a 2,10 oxygenated pinane is best determined from the chemical shift of the C9 methyl protons. The effect of a 2β-oxygen substituent is to deshield the C9 methyl protons, whereas a 2α-oxygen function has little effect, Table 4. This effect is discussed in greater detail later in this thesis.

Table 4

| | C8 | C9 |
|---|---|---|
| 2,10-epoxy-10α-pinane | 1.22 | 1.03 |
| 2.10-epoxy-10β-pinane | 1.23 | 0.92 |
| 10α-pinane-2,10-diol* | 1.26 | 1.09 |
| 10β-pinane-2,10-diol | 1.26 | 0.93 |
| 10α-pinan-2-ol | 1.22 | 1.09 |
| 10β-pinan-2-ol | 1.24 | 0.95 |

The reactions in this section are outlined in fig. 15.

Footnote: * The NMR spectrum of this diol is deduced from a mixture of epimeric diols described on p. 54 of this thesis.

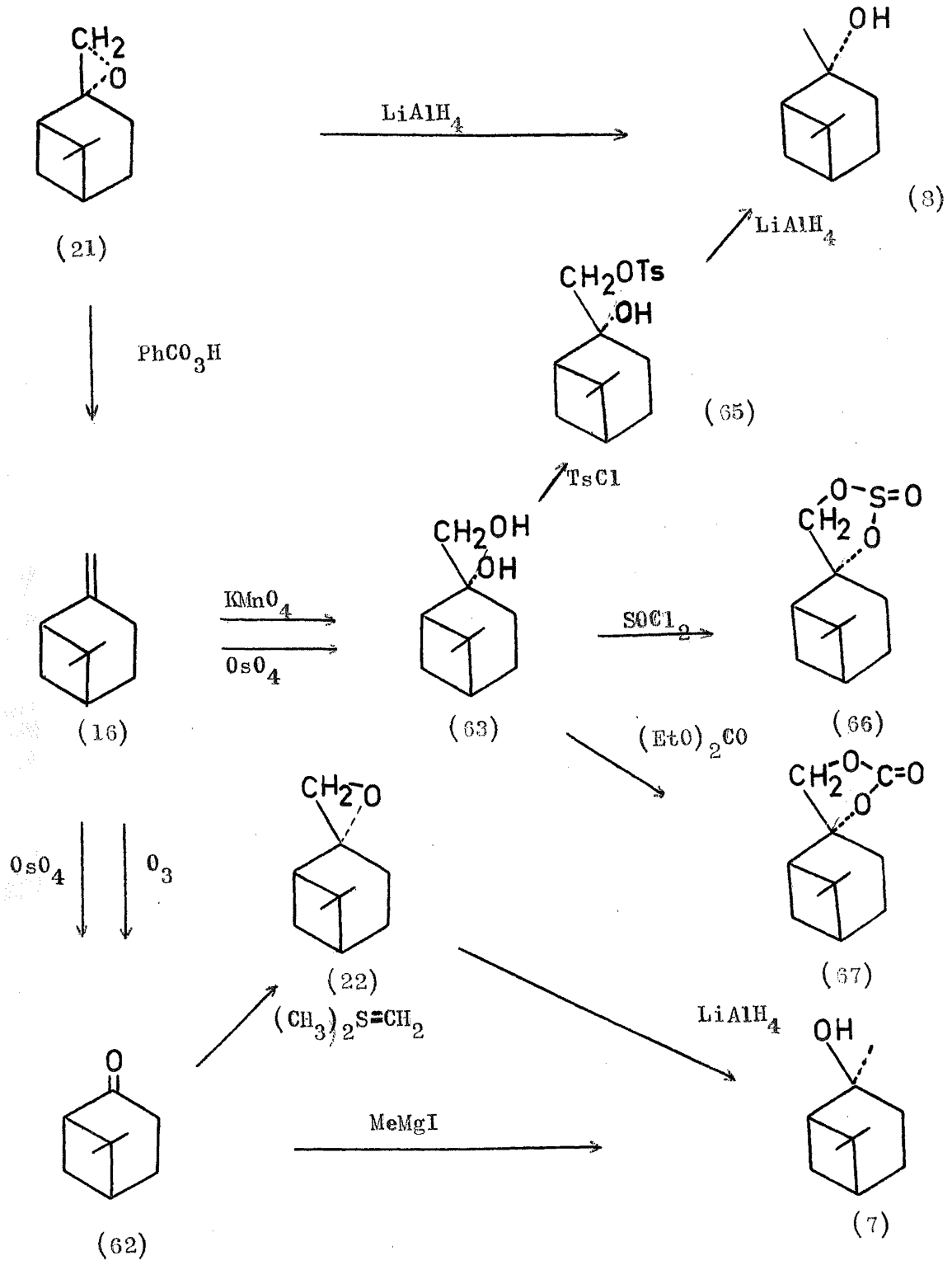

CH2
O
LiAlH4
OH
(8)
(21)
LiAlH4
CH2OTs
OH
(65)
PhCO3H
TsCl
CH2OH
OH
KMnO4
OsO4
SOCl2
O-S=O
CH2
O
(16)
(63)
(66)
(Et0)2CO
CH2-O
CH2-O-C=O
O
OsO4
O3
(22)
(67)
(CH3)2S=CH2
LiAlH4
O
OH
MeMgI
(62)
(7)

Fig. 15

## Section 2 2,3-oxygenated pinanes

The reaction of α-pinene with dilute aqueous permanganate, in the presence of magnesium sulphate, gave mainly pinonic acid (2), m.p. 105°, and 10β-pinane-2α,3α-diol (27) m.p. 40°. The ketol (25; 10β-pinan-3-on-2-ol) was detected in the mother liquor from the recrystallisation of the pinonic acid.

The oxidation of α-pinene by the literature method with powdered potassium permanganate gave the ketol (25) in good yield. Reduction of this ketol (25) by aluminium isopropoxide - isopropanol gave in addition to starting material, 10α-pinan-3-one (48), identified by comparison of its NMR spectrum with that of an authentic sample, and 10β-pinane-2,3α-diol, m.p. 46°, identical with the sample above by its NMR and IR spectrum.

Reduction of the ketol (25) with lithium aluminium hydride gave the epimeric diol (26; 10β-pinane-2,3β-diol), m.p. 153°.

The configuration of the diols at C2 is confirmed by their NMR spectra, Table 5.

The chemical shift values of the C9 methyl protons show these to be shielded relative to 10β-pinane, as expected for a 2α-oxygen function (see tables 4 and 12 and discussion thereof). The slight increase in the

Table 5

| | C8 | C9 | C9 |
|---|---|---|---|
| 10β-pinane-2,3α-diol (27) | 1.26 | 0.93 | 0.09 |
| 10β-pinane-2,3β-diol (26) | 1.25 | 0.95 | 0.11 |
| 10β-pinane | 1.20 | 1.02 | 0.18 |

3β-hydroxydiol (26) relative to the 3α-hydroxydiol (27) is consistent with the assigned 3β-configuration of this diol (see NMR section).

On treatment with thionyl chloride in pyridine and ether the diol (27) gave a crystalline cyclic sulphite, m.p. 60 - 64°. Although the cyclic sulphite gave an analysis consistent with pure cyclic sulphite, and the compound hydrolysed in high yield with aqueous-methanolic sodium hydroxide to give 10β-pinan-2,3α-diol (27), the NMR spectrum was not consistent with the sulphite being a pure compound. Fractional crystallisation from pentane afforded two distinct compounds 'A', m.p. 50 - 52° and 'B', m.p. 102°. These were subsequently shown to be present in a 1:1 ratio in the crude cyclic sulphite mixture. In view of the recovery (76%) of pure 10β-pinane-2,3α-diol (27) from the hydrolysis of the crude cyclic sulphite and the probable mechanism of formation of the cyclic sulphite

on reaction of diol (27) with thionyl chloride, it seemed probable that the isomerism arose from the geometry of the sulphite system in relation to the carbon skeleton. The NMR spectra, table 6, of the two isomers supported this postulate.

Table 6

| | C8 | C9 | C10 | 3βH | |
|---|---|---|---|---|---|
| cyclic sulphite Isomer A (68) | 1.33 | 0.93 | 1.78 | 4.90 | $J^{H^{3\beta}H^{4\beta}} = 7$ cps<br>$J^{H^{3\beta}H^{4\alpha}} = 2$ cps |
| cyclic sulphite Isomer B (69) | 1.38 | 0.91 | 1.41 | 4.65 | J = 8 cps<br>J' = 6 cps |
| cyclic carbonate (70) | 1.35 | 0.88 | 1.53 | 4.50 | $J^{H^{3\beta}H^{4\beta}} = 8$ cps<br>$J^{H^{3\beta}H^{4\alpha}} = 2.5$ cps |

Application of the experimentally determined relationship between coupling constants (J) and dihedral angles ($\Phi$)[96] to the one proton quartet (3βH) for isomer A, allowed a unique dihedral angle solution ($C_3H$ vs. $C_4H$) which may be incorporated in the conformation, fig. 16a. The dihedral angle relationship is indicated by the Newman projection, fig. 16b, for the C4-C3 bond. This conformation, 16a, is one in which C3 is slightly 'down' from a planar structure.

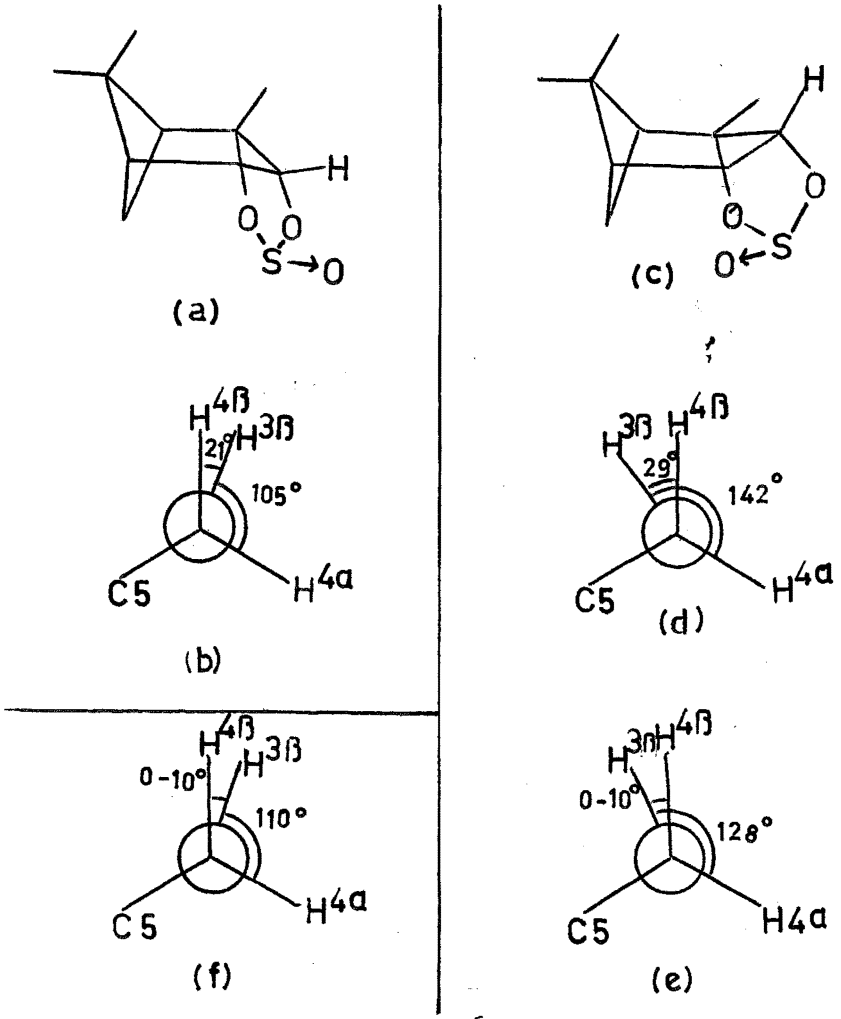



Fig. 16

Similar use of the relationship between J and for the B isomer affords two possible solutions. Both of these indicate that this isomer exists in a conformation slightly 'up' from planar, fig. 16c. The dihedral angle solutions are illustrated in the Newman projections fig. 16d and e.

As it seems unreasonable to expect the inter-conversion energy barrier between ring conformations 16a and 16c to be high enough for each to be isolated

by fractional crystallisation, it becomes necessary to suggest that these conformations are adopted as a consequence of the asymmetry of the sulphur atom of the cyclic sulphite moiety. The isomers A and B are assigned the structures 16a and 16b on the basis of minimum non-bonded interactions.

It should be noted here that a S = O bond, to a sulphur atom in a six-membered ring, tends to attain an axial configuration[97]. It seems unreasonable, however, to assume that this effect is due to the greater steric requirement of the S-atom lone pair compared with the S = O oxygen atom. For the purpose of the following discussion it is assumed that the oxygen atom is 'bigger' than the lone pair.

The slightly 'up' configuration of the B isomer is favoured, since in a 'down' conformation the non-bonded interaction between the S = O oxygen atom and the C7 methylene group is greater. A strictly planar conformation is not favourable as it would involve non-bonded interactions between the eclipsed groups attached to the C2, C3 and C4 carbon atoms. At the same time the constraint of the cyclic sulphite moiety prevents the attainment of extreme 'up' or 'down' conformations. In the A isomer the S = O oxygen C7 methylene interaction is absent. Consequently the 'down' conformation is favoured.

Recent results indicate that the anisotropic effects exhibited by a S = O bond of a sulphoxide and of a cyclic sulphite are similar to those associated with a triple bond[97], fig. 17a; whereas it had previously been assumed that these effects were similar to those of a C = C or a C = O bond[98], fig.17b.

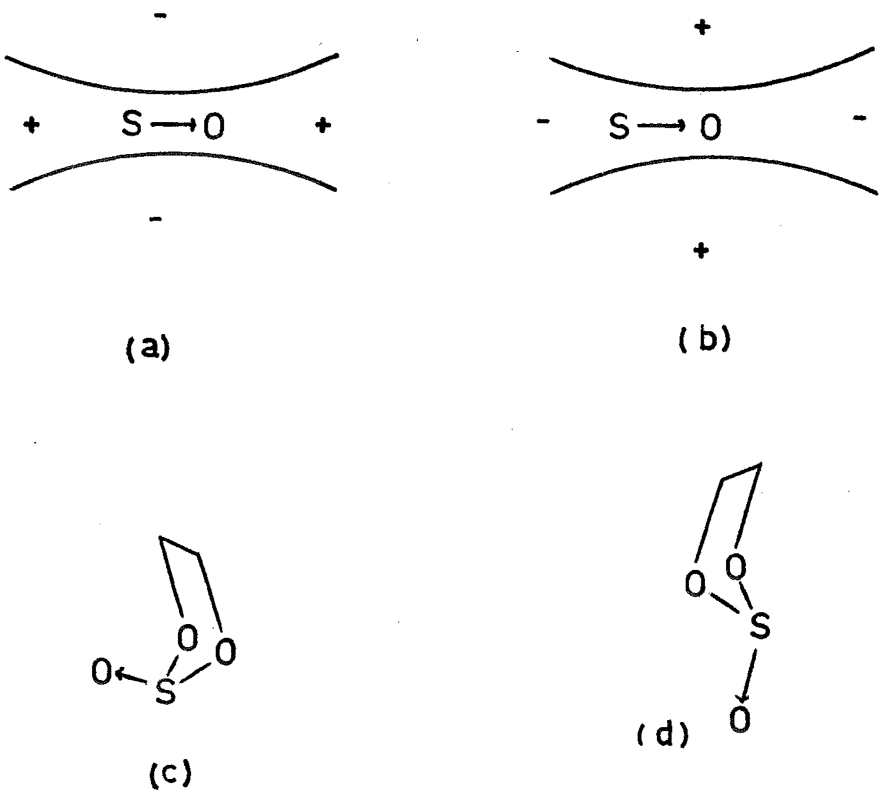



Fig. 17

If the triple bond anisotropy of the S = O bond is accepted, the shielded C10 methyl group of the B isomer must lie along the axis of the S = O bond. This defines the conformation of the sulphite ring such that the S = O bond is quasi-equatorial, fig.17d,

rather than quasi-axial, fig. 17c.

In the A isomer the C10 methyl group would be deshielded regardless of sulphite ring conformation.

10β-Pinane-2,3α-diol reacted with ethyl chloroformate in pyridine to give a solid crystalline cyclic carbonate (70), m.p. 82°. The NMR spectrum (table 6) indicated a pure compound with the structure above (70; 10β-pinane-2,3α-diol cyclic carbonate). The observed coupling constants for the 3βH, 4αH, 4βH system could be rationalised in terms of only one dihedral angle solution, with the ring conformation slightly 'down'. Dihedral angles are estimated as 0 - 10° and 110° (Newman projection fig. 16f).

In a thermal rearrangement, which will be described in detail in a later part of this thesis, the diol carbonate (70) gave a mixture of the known alcohols, trans-pinocarveol (20) and 10β-pin-3-en-2-ol (71). This clearly establishes the configuration of the diol as 10β-pinane-2,3α-diol (27) since the oxygen functions must retain their configuration in this reaction. The ease with which this diol forms cyclic sulphites and a carbonate is also consistent with a cis-relationship between the hydroxyl functions. Examination of models reveal the strain of formation of trans-sulphites or carbonate in this system to be prohibitive. Further support for the assignment of configuration of

the pinane-2,3-diols at the C3 position is provided in the next section.

## Section 3 2,3,10-oxygenated pinanes

Reaction of β-pinene (16) with lead tetraacetate followed by alkaline hydrolysis gave, after distillation, trans-pinocarveol (20) in 20% yield.

Because of the low yield obtained in this reaction an alternative method was investigated. Reaction of β-pinene with hydrogen peroxide (35% aqueous) in tert. butanol and in the presence of a catalytic amount of selenium dioxide (0.04 moles per mole reagent) gave trans-pinocarveol in 50% yield. Apart from the higher yield, this synthetic route is more convenient since it involves only one step, and no isomeric byproducts are formed. Pinocarvone (23) was initially prepared by oxidation by β-pinene with selenium dioxide (molar quantities). The yield obtained, 7.2%, was very low due to polymerisation during distillation.

In addition to the low yield, selenium dioxide and selenides, formed as byproducts, are toxic. The difficulty of separating the unstable product from the isomeric aldehyde, pin-2-en-10-al (24) which is a minor product also renders this reaction path undesirable.

Oxidation of trans-pinocarveol with activated

manganese dioxide gave pinocarvone in 85% yield. No further purification of this material was necessary.

cis-Pinocarveol (56) was made from pinocarvone in good yield either by Meerwein-Ponndorf-Verley reduction or by bromination followed by debromination-reduction with zinc powder.

Epoxidation of trans-pinocarveol with perbenzoic acid in ether gave 2,10-epoxy-10β-pinan-3α-ol (72), m.p. 15° in 63% yield. The IR spectrum showed an OH absorption at 3500 $cm^{-1}$ (O-H stretch). The NMR spectrum, table 7, was also consistent with this structure.

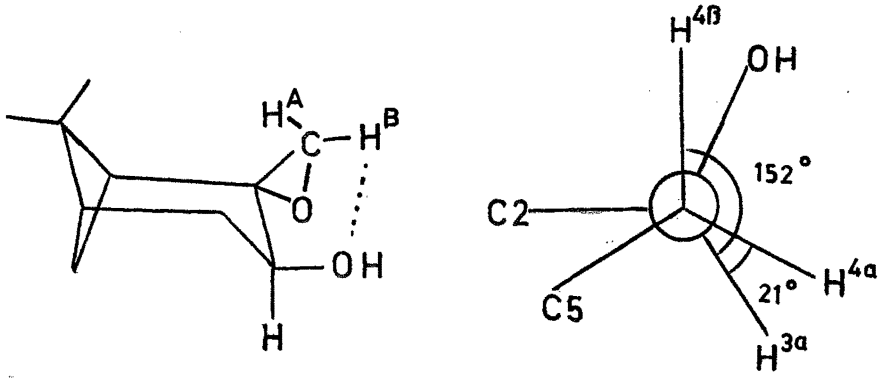
Epoxidation of cis-pinocarveol (56) under the same conditions gave 2,10-epoxy-10β-pinan-3β-ol (73), m.p. 6°. The IR spectrum and NMR spectrum (table 7) were consistent with the assigned structure. The NMR spectra of the two epoxides (72 and 73) indicated no epimeric epoxides in the former case and less than 8% in the latter case.

The C9 methyl protons have chemical shifts consistent with a 2α oxygen function. The 3β-hydroxy isomer has a slightly higher C9 chemical shift than the 3α isomer as would be expected (see previous section). No prediction can be made concerning the conformation of the 3α- isomer (72) since the 3β proton signal in the NMR spectrum is not clearly resolved.

Table 7

| | | | | |
|---|---|---|---|---|
| 2,10-epoxy-10β-pinan-3α-ol (72) | 3.79d | 1.28 | 0.87 | 2.77 ($\Delta\nu$ = 0.18 ppm) ($J_{AB}$ = 5 cps) |
| 2,10-epoxy-10β-pinan-3β-ol (73) | 4.21 ($J^{4\alpha,3\alpha}$ = 7 cps) ($J^{4\beta,3\alpha}$ = 9.5 cps) | 1.27 | 0.92 | 2.82 ($\Delta\nu$ = 0.83 ppm) ($J_{AB}$ = 5 cps) |
| 2,10-epoxy-10β-pinan-3-one (74) | | 1.38 | 0.97 | |
| 2,10-epoxy-10α-pinan-3-one (75) | | 1.37 | 1.03 | |

The coupling constants ($J^{3\alpha,4\alpha}$ = 7; $J^{3\alpha,4\beta}$ = 9.5) found for the 3β-hydroxy isomer (73) are consistent with dihedral angles of 152 and 21° indicating a 'down' conformation.



This conformation is further supported by the deshielding of the C10B proton, above ($\Delta\nu$ C10 protons = 0.83 ppm) relative to the C10B proton in the epimeric epoxide (72; $\Delta\nu$ = 0.18 ppm).

Reduction of 2,10-epoxy-10β-pinan-3α-ol (72) with lithium aluminium hydride gave 10β-pinane-2,3α-diol (27), identical to the product produced by cis-hydroxylation of α-pinene. This confirms the assignment of the diol since the configuration of the hydroxyl group at C3 of trans-pinocarveol, and hence the epoxide derived from trans-pinocarveol, is known to be 3α-.

At the same time, since the configuration of the oxygen function in epoxide (72) must be retained during the reduction, the configuration of the epoxide (72) at C2 is confirmed.

Reduction of 2,10-epoxy-10β-pinan-3β-ol (73) under the same conditions gave 10β-pinane-2,3β-diol (26) confirming the structure assigned to the epoxide.

The α-side epoxidation of cis-pinocarveol is interesting in that it involves epoxidation on the side opposite to the hydroxyl group.

It has previously been found[99] that a hydroxyl group tends to direct the epoxidising agent on to the same face as the hydroxyl group. It should be noted here that since the epoxidation of cis-pinocarveol

was carried out in a polar solvent, ether, the directional effect of the hydroxyl group is not as great as in a nonpolar solvent. Additionally this effect is overruled by the steric hindrance to attack on the β-face of a pinane.

Reaction of pinocarvone (23) with alkaline hydrogen peroxide, according to the conditions of Klein and Ohloff[38] provided an oil shown by NMR spectroscopy to consist of a 7:3 mixture, assumed to be the 2,10-epoxypinan-3-ones (74 and 75).

Reduction of the epoxide mixture with lithium aluminium hydride afforded a complex mixture of diols containing ca. 30% 10β-pinane-2,3α-diol (27; by g.l.c.).

The major compound in the epoxide mixture was identified as 2,10-epoxy-10β-pinan-3-one (74), since oxidation of 2,10-epoxy-10β-pinan-3α-ol (72) with chromium trioxide in pyridine gave a compound with an NMR spectrum corresponding to the major product in the epoxide mixture. The minor product was assumed to be 2,10-epoxy-10α-pinan-3-one (75) from its mode of formation.

The product ratio can be rationalised in terms of the most stable rotamer of the intermediate enolate iron, fig. 18a, formed by hydroperoxide ion attack on pinocarvone.

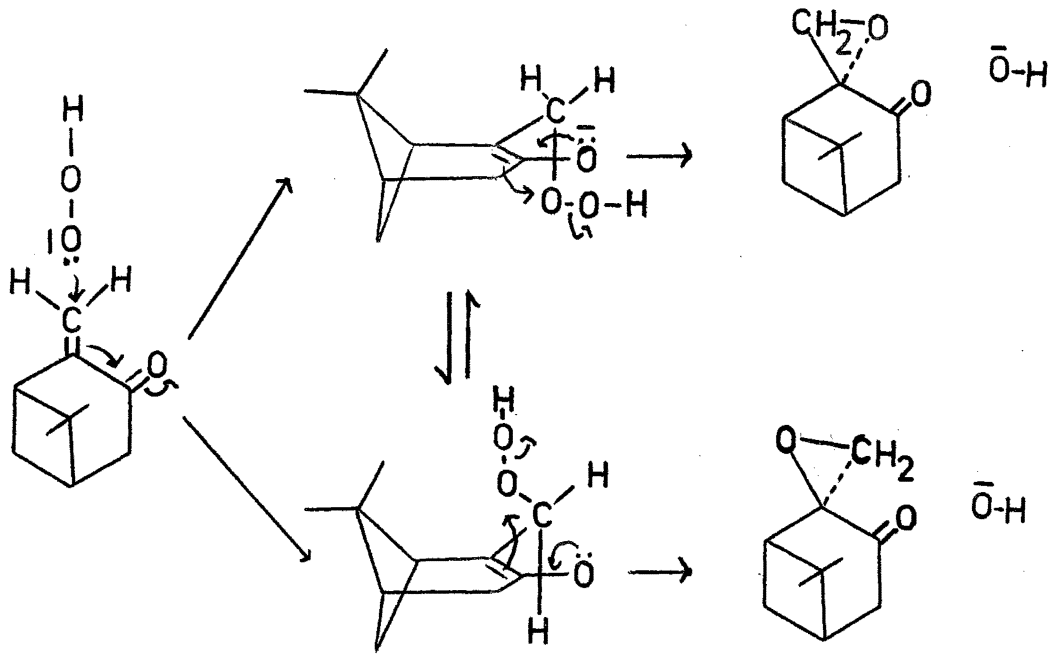


Fig. 18

The NMR data found, table 7, is consistent with the assignments above.

The C9 methyl group is less shielded in the β-epoxide (75) than in the α-epoxide as expected. This effect is, however, smaller than in the saturated epoxides (c.f. table 3), indicating that the keto epoxides exist in a more planar conformation, i.e. the 2β-group is less axial. The near planar structure is confirmed by the unusual long range deshielding of C8 methyl protons, indicating that these lie along the axis of the C = O bond. This effect defines the conformation as being slightly 'down' from planar.

# Chapter 2

## REARRANGEMENTS OF SUBSTITUTED PINANES

The rearrangements of pinanes involving carbonium ion formation of C2 have usually been discussed in terms of non-classical carbonium ions. Since it has not been possible, on the available evidence, to discern whether bridged ions exist as resonance stabilised intermediates, non-classical ions, or as a high energy transition state between one discrete carbonium ion and another, the latter, and more simple concept, will be used in this thesis. It should be noted that this concept is adequate to explain fully the results discussed later.

### Section 1 The rearrangement of 2,10-oxygenated pinanes

The rearrangement of 2,10-epoxy-10β-pinane (21) has been studied under a number of conditions. It was hoped that an examination of the reactions of this epoxide together with 2,10-epoxy-10α-pinane (22) under the same conditions would indicate the extent of carbonium formation in the acid catalysed opening of the epoxides.

The two epoxides were treated with a number of acidic reagents in solvents of differing polarity and the ratio of products estimated by integration of the

NMR spectrum of the crude material. In general three products were formed, the two pinan-10-als and a non-volatile polymer.

The configuration of the aldehydes was confirmed by independent synthesis, involving oxidation of the two pinan-10-ols obtained by hydroboration of β-pinene[16].

The structure of the aldehyde was further confirmed by reduction of an aldehyde mixture, obtained in an acid catalysed rearrangement of the epoxide (21), with sodium borohydride, to give a mixture of the corresponding pinan-10-ols.

In general the reaction gave yields of aldehydes of ca. 50% in a polar solvent such as ether; but in non-polar solvents such as pentane only traces of the two aldehydes were found. The yields in benzene were ca. 20%.

On reaction with boron trifluoride etherate in ether 2,10-epoxy-10α-pinane gave 10α-pinan-10-al (49) and 10β-pinan-10-al (52) in the ratio 34:66 whereas 2,10-epoxy-10β-pinene gave a 40:60 ratio. In general both epoxides gave an approximately 1:1 ratio of the two aldehydes on reaction with boron trifluoride etherate in various solvents, for details see table 14. Reaction with sulphuric acid in ether gave mainly

10β-pinan-10-al (52), 79 - 88% of total aldehyde content, but the yield of aldehyde to total product was only low, 7 - 13%.

Since both epoxides give nearly the same ratio of products it must be assumed that the reaction involves complete carbonium ion formation. An enol intermediate may be excluded since neither epimeric aldehyde was affected by treatment with $BF_3$ under the reaction conditions. Equilibration of the aldehydes should lead to a high ratio of the thermodynamically more stable 10α-pinan-10-al to 10β-pinan-10-al (Equilibration of the pinan-3-ones leads to a 3:1 ratio of 10α-pinan-3-one to 10β-pinan-3-one).

The reaction is thought to proceed through a discrete ion of C2, fig. 19, allowing free rotation about the C2-C10 bond. The aldehydes are then formed by a 1 -2 hydride shift.

The preferential formation of the thermodynamically less stable aldehyde, 10β-pinan-10-al, fig. 19e, is probably due to the higher energy of the transition state for the formation of 10α-pinan-10-al, fig. 19c, due to the steric hindrance of the geminal dimethyl group to β-face hydride shift, fig. 19b.

It is thought that in those reactions where one aldehyde is obtained, the other aldehyde was initially formed but was removed by further reaction. It has

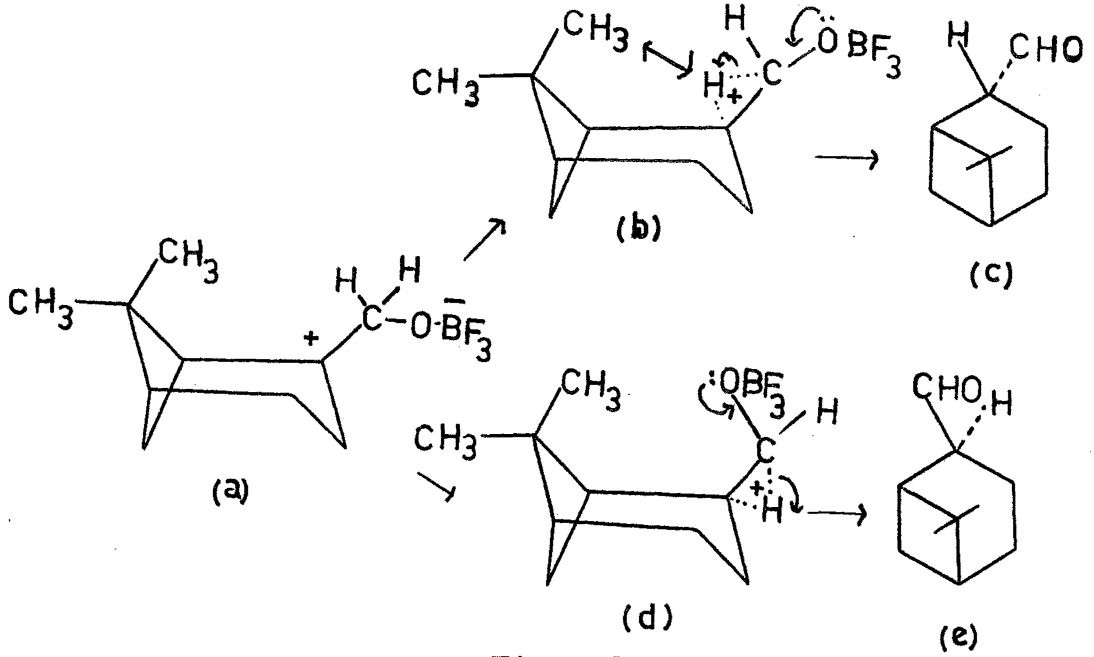



Fig. 19

been found that a mixture of pinan-10-als left standing for some time contains no 10β-pinan-10-al (52) but a mixture of 10α-pinan-10-al (49) and p-menth-1-ene-7-al (51). The compounds were identified, after separation by preparative g.l.c., by examination of their NMR spectra.

The reaction of 2,10-epoxy-10β-pinane with sulphur dioxide in pyridine gave a complex mixture of cyclic sulphites and unsaturated alcohols. The product mixture was treated with a solution of sodium hydroxide in methanol-water to hydrolyse any sulphite present. The major components of the resulting mixture were separated by column chromatography.

The compounds in order of elution, were found to be pin-2-en-10-ol (50), (identified by comparison of its spectra with that of an authentic compound), p-mentha-1,8-dien-7-ol (76; perrilyl alcohol) and a diol mixture consisting mainly of 10β-pinane-2,10-diol (63).

Reaction of 2,10-epoxy-10α-pinane (22) with sulphur dioxide and pyridine under the same conditions followed by hydrolysis gave similar products. The diol mixture obtained from this epoxide constituted a 1:1 ratio of compounds. Formation of the tosylates of this diol mixture followed by reduction with lithium aluminium hydride afforded a mixture of 10α-pinan-2-ol (7) and 10β-pinan-2-ol (8), proving the diol mixture to consist of 10α-pinane-2,10-diol (64) and 10β-pinane-2,10-diol.

By combining the values from integration of the NMR spectra of the diol mixtures and g.l.c. analyses of the alcohol diol mixtures the relative amounts of product could be assessed quantitatively, table 8.

Since both epoxides give a mixture of diols the intermediate, in the formation of the corresponding cyclic sulphites, must be a discrete ion allowing rotation of the C2-C10 bond. The fact that both sulphites are formed in each case indicates that the rates of rotation and of recombination are of the same order.

Table 8

| Products | 2,10-epoxy-10α-pinane | 2,10-epoxy-10β-pinane |
|---|---|---|
| pin-2-en-10-ol | 29 | 20 |
| p-mentha-2,8-dien-7-ol | 6 | 19 |
| 10α-pinane-2,10-diol | 27 | 13 |
| 10β-pinane-2,10-diol | 29 | 37 |

From the difference in the yields of p-mentha-2,8-dien-7-ol it is seen that the configuration of the epoxide determines the extent of $C_1$-C6 bond rupture. However, since this product is formed from both epoxides concertion of epoxide opening and $C_1$-C6 bond rupture cannot be a requirement for this reaction. The intermediate complexes formed with sulphur dioxide and 2,10-epoxy-10α-pinane (22) and 2,10-epoxy-10β-pinane (21) are expected to exist in the 'up' and 'down' conformation respectively, to achieve minimum non-bonded interactions, fig. 20a and b.

These complexes would give rise to the same carbonium ion; but in the 'up' and 'down' conformation respectively. From fig. 20c and d it can be seen that C6-$C_1$ rupture is favoured in the carbonium ion with a 'down' conformation, fig. 20d since in this conformation the C6-$C_1$ bond is eclipsed with the

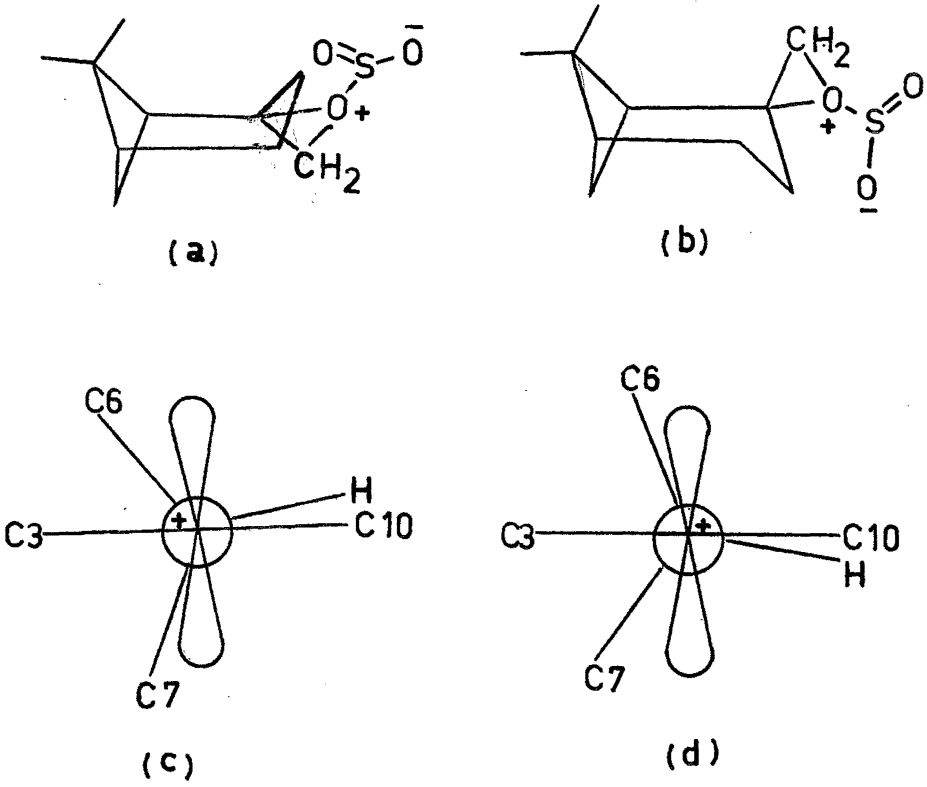



Fig. 20

vacant p-orbital of the carbonium ion. C6-C1 bond rupture is not favoured in the 'up' conformer, fig. 20c, derived from the complex 20a.

It is pertinent to note here that although C7 migration is favoured in the 'up' conformation; migrations do not take place without the presence of a nucleophile.

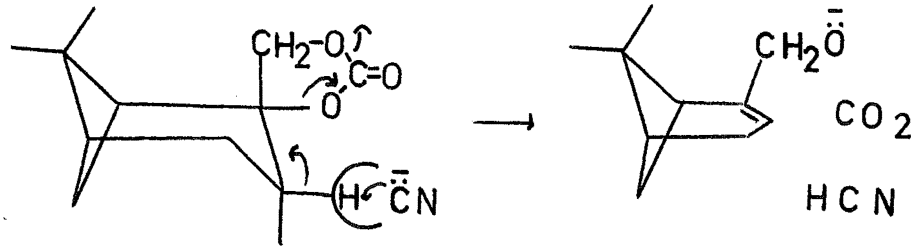
The relative amounts of p-mentha-2,8-dien-7-ol from 2,10-epoxy-10α-pinane and 2,10-epoxy-10β-pinane on reaction with sulphur dioxide can be rationalised in terms of the initial formation of a carbonium ion in the 'up' and 'down' conformation respectively

providing the rate of interconversion between the two carbonium ions is of the same order as the rate of rupture of the C1-C6 bond.

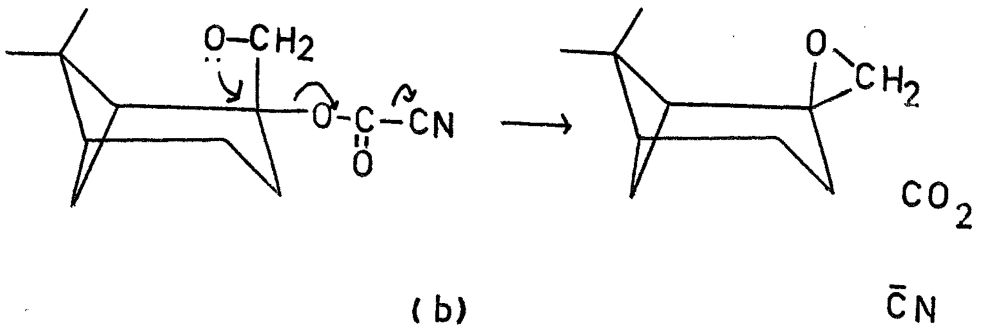
On refluxing in pyridine for 2 hours the cyclic sulphite (66) from 10β-pinane-2,10-diol rearranged to give a 53:19:28 ratio of 10β-pinan-10-al (52), 10α-pinan-10-al (49) and pin-2-en-10-ol (50). It is interesting to note, that although rotation about the C2-C10 bond must be possible, in the intermediate, and the carbonium ion expected from ring opening of the cyclic sulphite (66) should be initially identical to the carbonium ion derived from sulphur dioxide attack on the epoxide (21), the products obtained are radically different. This effect is not understood, but it is thought that the difference in temperature, (room temp. to refluxing pyridine) is in some way responsible.

Similar reactions were carried out at the same temperature. On heating the cyclic sulphite (66) in carbowax at ca. 200° and 50 mm only a low yield of p-cymene (77; 4-isopropyl-methylbenzene) and α,p-dimethyl -styrene (78) was obtained. The epoxide (21) heated in a stream of $SO_2$ under the same condition gave similar products. Due to the low yields of the formation of these products, it is not considered possible to draw mechanistic conclusions.

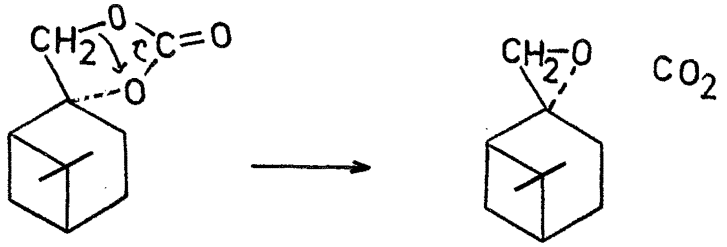
When heated in carbowax , in the presence of potassium cyanide, 10β-pinan-2,10-diol cyclic carbonate (67) gave an oil, which was shown, by comparison of its NMR spectrum with those of authentic samples, to consist of a 30:70 mixture of 2,10-epoxy-10 -pinane (21) and pin-2-en-10-ol (50). The epoxide can not arise from an alkoxide intermediate, fig.21b similar to that postulated by Searles and Hummel[58], since such an intermediate would lead to inversion at C2. The reaction is thought to involve internal collapse of the carbonate moiety, fig. 21 c. The unsaturated alcohol (50) can be formed by base attack at a C3 proton concerted with elimination and ring opening, fig. 21 a.




(a)




(b)



(c)

Fig. 21

## Section 2 The rearrangement of 2,3-oxygenated pinanes

The formation of 2,2,4-trimethylcyclopent-3-en-1-acetaldehyde (77) and 10αpinan-3-one (48) in addition to 2,2,3-trimethylcyclopent-3-ene-1-acetaldehyde (47) from the reaction of zinc bromide on 2,3-epoxy-10β-pinane[78] (19) has been disputed by Lewis and Hedrick[79]. Repetition of this reaction yielded a product containing largely 2,2,3-trimethylcyclopent-3-ene-1-acetaldehyde (47; 96%) but no 10α-pinan-3-one or aldehyde (79) in agreement with the results of Lewis and Hedrick.

The thermal rearrangement of the 10β-pinane-2,3α-diol sulphites (68 and 69) was carried out by heating the cyclic sulphites in carbowax 400 to ca. 200° at 50 mm. pressure so that the products distilled off. The distillate (ca. 80% recovery) was shown by g.l.c. to consist of a 98:2 mixture of 10α-pinan-3-one (48) and 2,2,3-trimethylcyclopent-3-en-1-acetaldehyde (47).

Reaction of 2,3-epoxy-10β-pinane with sulphur dioxide gas in carbowax 400 at 200° at 50 mm. gave a distillate which appeared by g.l.c. to consist of five compounds, in the ratio 10,11,22,55 and 2%. The five fractions were isolated by preparative g.l.c. The structures assignments to these compounds are listed in table 9.

Fraction 1 was identified as the hydrocarbon (80) from its U.V. spectrum (λmax 265 mμ - compare α-phellandrene (81), λmax 263 mμ) and its NMR spectrum which exhibited signals at 1.74 (6H; C7 and C9 methyl groups), 4.75 (2H; C10 methylene protons), 5.42 (1H; C2 vinylene proton) and 5.74 (2H; C3 and C6 vinylene protons). This compound was found to isomerise to p-cymene on standing.

Fraction 2 was shown to consist of p-cymene by comparison of its NMR spectrum with a literature spectrum[100].

Fraction 3 was shown to consist of a mixture of an aromatic hydrocarbon and an aldehyde by its NMR spectrum. The aldehyde was removed as its bisulphite complex and the hydrocarbon isolated.

From its NMR spectrum which exhibited signals at 2.12 (3H; α-methyl protons), 2.33 (3H; p-methyl protons), 4.98 and 5.22 (1H each; methylene protons) and 7.19 ppm (4H, A.B. quartet, aromatic protons) the compound was assigned the structure (78),

Table 9

| Fraction | Composition | Yield % |
|---|---|---|
| 1 | 1-isopropylpylidene-4-methyl-cyclohexa-2,4-diene (80) | 10 |
| 2 | p-cymene (77) | 11 |
| 3 | α,p-dimethylstyrene (78) | 7 |
| | 2,2,4-trimethylcyclopent-3-en-1-acetaldehyde (79) | 15 |
| 4 | 2,2,3-trimethylcyclopent-3-en-1-acetaldehyde (47) | 55 |
| 5 | Pinocamphone (48) | 2 |

α,p-dimethylstyrene.

The aldehyde was identified as 2,2,4-trimethylcyclopent-3-ene-1-acetaldehyde (79) from its NMR spectrum and retention time relative to fraction 4. Relative yields of hydrocarbon and aldehyde were determined from the NMR spectrum of the mixture.

Fraction 4 was identified as 2,2,3-trimethylcyclopent-3-en-1-acetaldehyde (47) by comparison of its NMR spectrum with literature values[79].

Fraction 5 was identified as 10α-pinan-3-one by comparison of its NMR spectrum with that of an authentic sample.

The markedly different product compositions of the cyclic sulphite pyrolysis reaction, and the

epoxide-sulphur dioxide reaction must be discussed in the context of the following additional information. In the absence of sulphur dioxide gas the epoxide (19) distills unchanged and 10α-pinan-3-one (48) does not rearrange to aldehyde (47), or aldehyde (47) to pinan-3-one in the presence of sulphur dioxide at 200°.

For the pyrolysis of the cyclic sulphite mixture it seems probable that early in the process of breaking the C2-O bond, the reacting molecule would move towards a slightly 'up' conformation, fig. 16c, in which the 3β-hydrogen atom would be well placed for migration to the 2β-position concerted with C2-O bond cleavage. In contrast to this limited but significant rotational mobility which can be accommodated by the flexible cyclic sulphite ring system, the conformations energetically available to 2,3-epoxy-10β-pinane (19) during its 'Lewis Acid' catalysed rearrangement are limited severely by the constraint imposed by the attachment of the leaving group directly to C3.

For maximum residual solvation of the developing C2 carbonium ion by the departing oxygen atom of the epoxide, the axial cleavage mode of reaction would be followed to give the carbonium ion (82) at full charge separation. Throughout this process of charge separation in the C2-O bond the C3-H bond would be maintained in the plane of the developing C2

carbonium ion - not a favourable position for migration of the 3β-H. Consequently C6 migration which is favoured by a 'down' conformation occurs, see fig. 20 b and d. C7 migration and C3- hydride migration can occur by a collapse of this conformation.

The rearrangement of 2,3-epoxy-10β-pinane apparently constitutes exception to the observation that a C6 or C7 methyl shift does not occur in the absence of a nucleophile. However, the products derived from this rearrangement are quite unique. Since no substituted bornanes are derived it seems probable that the C6 to C2 shift is required to be concerted with the collapse of the C2-C3 bond, fig. 22a; rather than formation of a discrete bornyl ion followed by collapse of the C2-C3 bond, fig. 22b.

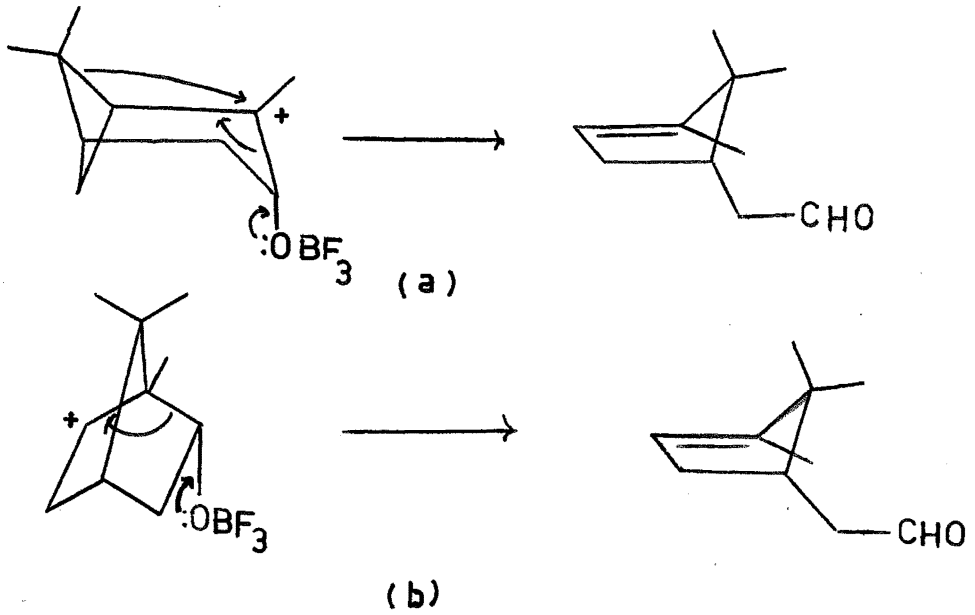



Fig. 22

Since the stereochemistry of the glycol derived by permanganate hydroxylation of α-pinene has now been established beyond doubt, it seems pertinent to discuss the rearrangement of this glycol (10β-pinan-2,3α-diol; 27) with sulphuric acid carried out by Schmidt et al.[46]

As the diol (27) has a 2α- hydroxyl group the removal of the hydroxyl group cannot be concerted with an alkyl shift since this would give rise to a compound of the bornane series, whereas the fenchane diol (28) is obtained. The rearrangement must proceed through a discrete ion at C2, fig. 23a. The specificity for C7 migration as opposed to C6 migration is considered to arise as a result of the preferred 'up' conformation of this ion, fig. 23a.

In this conformation the vacant p orbital at C2 is nearly eclipsed with the C7-C1 bond, fig. 20c, a favourable situation for C7 migration.

It has previously been found that skeletal rearrangement of compounds with a 3α-hydroxyl group lead to the formation of fenchanes; whereas 3β-hydroxy compounds rearrange to give bornanes, see introduction. It appears that these results can be rationalised by consideration of the preferred conformation of the intermediate carbonium ions. Whereas a 3α-hydroxyl group gives rise to an 'up'

conformation of the carbonium ion; a 3β-hydroxyl group directs the skeleton into a 'down' conformation, fig. 23b, in which C6 migration is favoured, see fig. 20d.

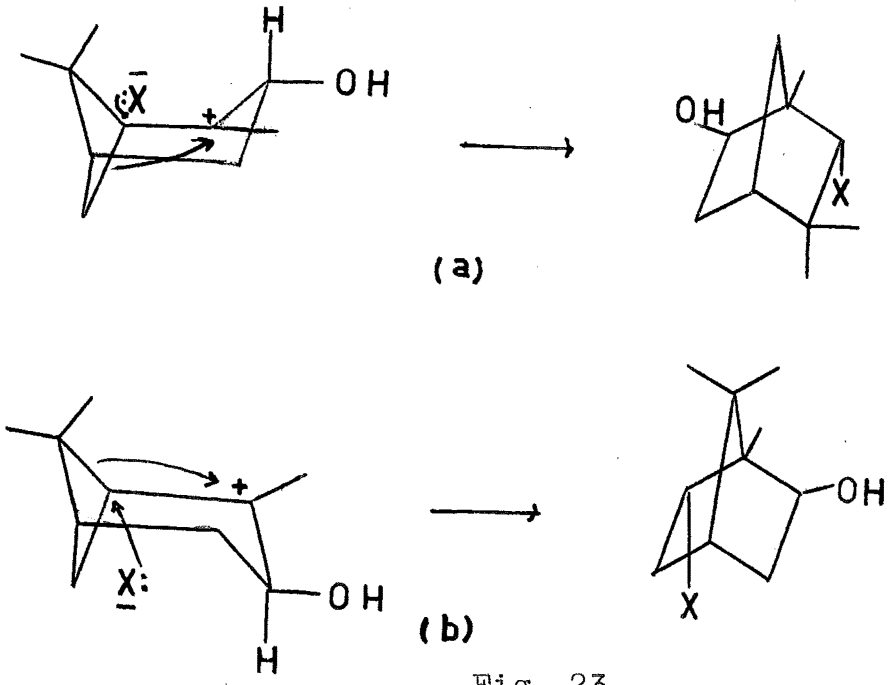



Fig. 23

Section 3 The rearrangement of 2,3,10-oxygenated pinanes

The reaction of 2,10-epoxy-10β-pinan-3α-ol (72) with catalytic amounts of p-toluenesulphonic acid in methanol gave an oil which appeared to consist of two major compounds, by t.l.c. The compounds were separated by adsorbtion onto an alumina column and elution with pentane-ether. The first fraction

(40% of recovered material) had an NMR spectrum which was not consistent with a monomer. A mass spectrum indicated a mixture of compounds, although the fraction appeared pure by t.l.c. Mass numbers of 302 and 567 pointed to dimerisation and trimerisation. This fraction was not investigated further. The second fraction (42% of recovered material) was assigned the structure (fig. 24b; 2 endo-methoxyfenchane-6 exo,10-diol) on the basis of its NMR spectrum; which had signals at 0.91 and 1.09 (3H each; C8 and C9 methyl protons), 1.43 to 1.73 (4H multiplet; C4, C5 endo and C7 protons), 2.34 (1H octet; C5 exo proton, $J^{C6H}$ = 3 cps, J' = 13 cps J" = 7 cps), 2.97 (2H, OH protons), 3.10 (1H; C2 proton), 3.34 (3H; methoxy protons), 3.90 (2H; C10 methylene protons) and 4.33 ppm (1H; quartet, $J^{C5\,exo-H}$ = 3 cps, $J^{C5\,endo-H}$ = 7 cps).

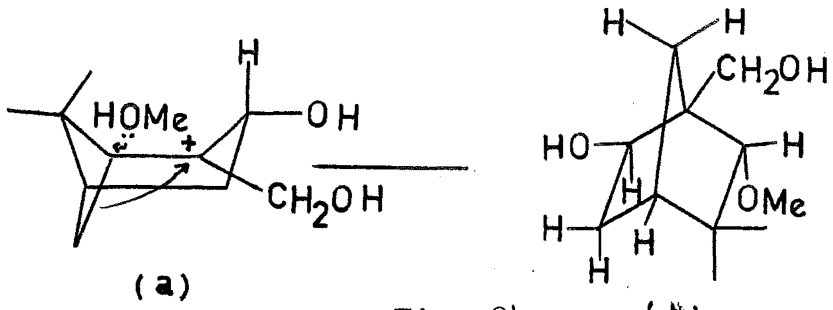



Fig. 24

The methoxy group is assigned the endo- configuration on the basis of the known mode of reaction of pinanes to give endo attack[84, 101], the exceptional deshielding of the vicinal 6-endo proton and the absence of coupling effects expected for a C2-C6 endo-endo proton system. The C6 hydroxyl group is assigned the exo- configuration, which corresponds to retention of configuration, on the basis of the peak shape of the C6 proton with those of authentic spectra of exo- and endo- isofenchol. The peak found for an exo proton is considerably broader than the peaks found for the endo protons.

The mode of rearrangement is in accord with the postulate, in the previous section, that the 3α-hydroxyl group will direct the intermediate carbonium ion, fig. 24a, into an 'up' conformation. Consequently the favoured C7 migration will take place to give the product fig. 24b. The C10 hydroxy methylene group, derived by opening the epoxide (72) with acid, is not expected to affect the conformation of the carbonium ion; since in both 'up' and 'down' conformations it remains quasi-equatorial.

Under identical reaction conditions the epoxide (73; 2,10-epoxy-10β-pinan-3β-ol) gave an extremely complex reaction mixture, six major and six minor compound by t.l.c. Some partial success was

achieved in separating these fractions; but the NMR spectra of samples, pure by t.l.c., were not consistent with pure monomeric compounds. This reaction was not investigated further.

# APPENDIX A

## Mercuration of β-pinene

A convenient synthesis of alcohols from alkenes, by oxy-mercuration followed by reduction with sodium borohydride, has recently been reported[102]. The alcohol formed is that equivalent to Markovnikoff addition of water to a double bond. The stereochemistry of the addition is such that the resulting hydroxyl group is on the least hindered side of the molecule.

It was thought that starting from β-pinene this might provide a convenient route to 10β-pinan-2-ol (8).

Reaction of α- and β-pinene, with mercuric acetate in dry acetic acid has been found[103] to give essentially the same yields of 10-acetoxypin-2-ene (84), p-cymene (77) and sobrerol diacetate (85; 6,8-diacetoxy-p-menth-1-ene). The major product, 10-acetoxypin-2-ene, is thought to arise via the formation of a mesomeric free radical, fig. 25.

The reaction of β-pinene with mercuric acetate, followed by reduction with sodium borohydride gave an oil which did not exhibit a band characteristic of an alcohol in the IR spectrum.

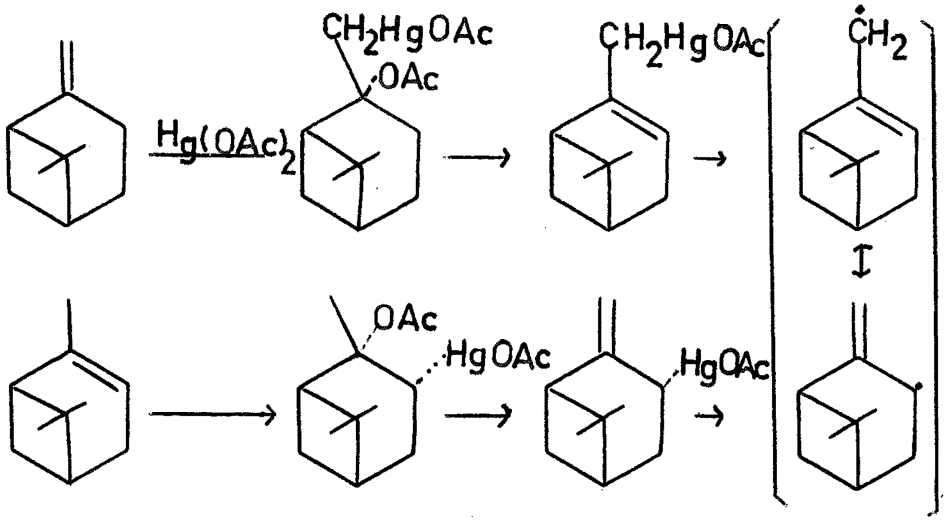



Fig. 25

Although the NMR spectrum seemed to indicate a mixture of α- and β-pinene g.l.c. showed the major fraction of the reaction product to be eluted much later than these compounds.

Isolation of this major high-boiling fraction by fractional distillation afforded an oil, which, although appearing pure by g.l.c., had an NMR spectrum that was only consistent with a mixture. The fraction was shown to consist of hydrocarbon dimers by means of molecular weight determinations by Rast's method and use of an osmometer. Micro-analytical results gave an empirical formula of $(C_2H_3)_n$ consistent with mass spectral data which indicated a molecular weight of 270.

The NMR spectrum exhibited methyl proton signals at 0.83 (C9 methyl) and 1.27 (C8 methyl),

regions associated with a pinane skeleton, and C=C<u>H</u>- and C=C<u>H$_2$</u> proton signals in the ratio 4:3. On this basis the reaction product from mercuration of β-pinane is thought to consist of a mixture of dimeric isomers, fig. 26. The isomer, 26a, must be predominant to rationalise the proton integral ratio above.

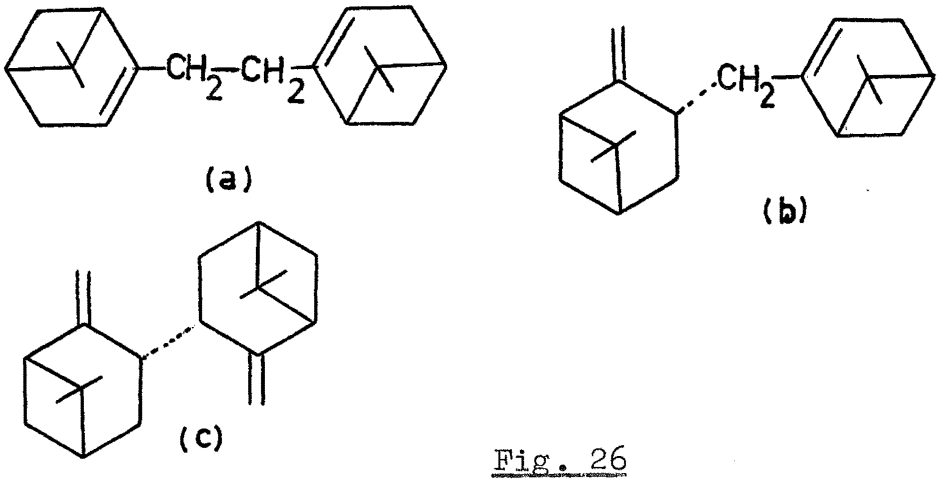



Fig. 26

These products probably arise by the dimerisation of the mesomeric free radical previously postulated[103], fig. 25.

# APPENDIX B

## The alkali catalysed rearrangement of the 2,10-epoxy-10β-pinan-3-ols

Introduction: During the study of the chemistry of the epoxy alcohols (72 and 73) an unexpected alkali catalysed rearrangement of these epoxy alcohols was found, which yielded pinocarvone (23) as the sole product.

There is no precedent for this alkali catalysed type of reaction. In a recent publication the acid catalysed rearrangement[104] of analogous epoxy alcohols, fig. 27a and d, was described. The authors proposed a mechanism involving acid catalysed opening of the epoxides concerted with a 1-2 hydride shifts, to give the 3-hydroxyketones, fig. 27 b and e. These were then proposed to eliminate to give the corresponding conjugated ketones, fig. 27 c and f. The acid catalysed elimination of a 3-hydroxy ketone is a well established reaction[105].

Results: 2,10-Epoxy-10β-pinan-3α-ol (72) rearranged on refluxing with a 1.7M solution of sodium hydroxide in methanol-water (2:1) to give an oil. This material was shown by comparison of its NMR spectrum with those of authentic samples to consist of a 1:1 mixture of

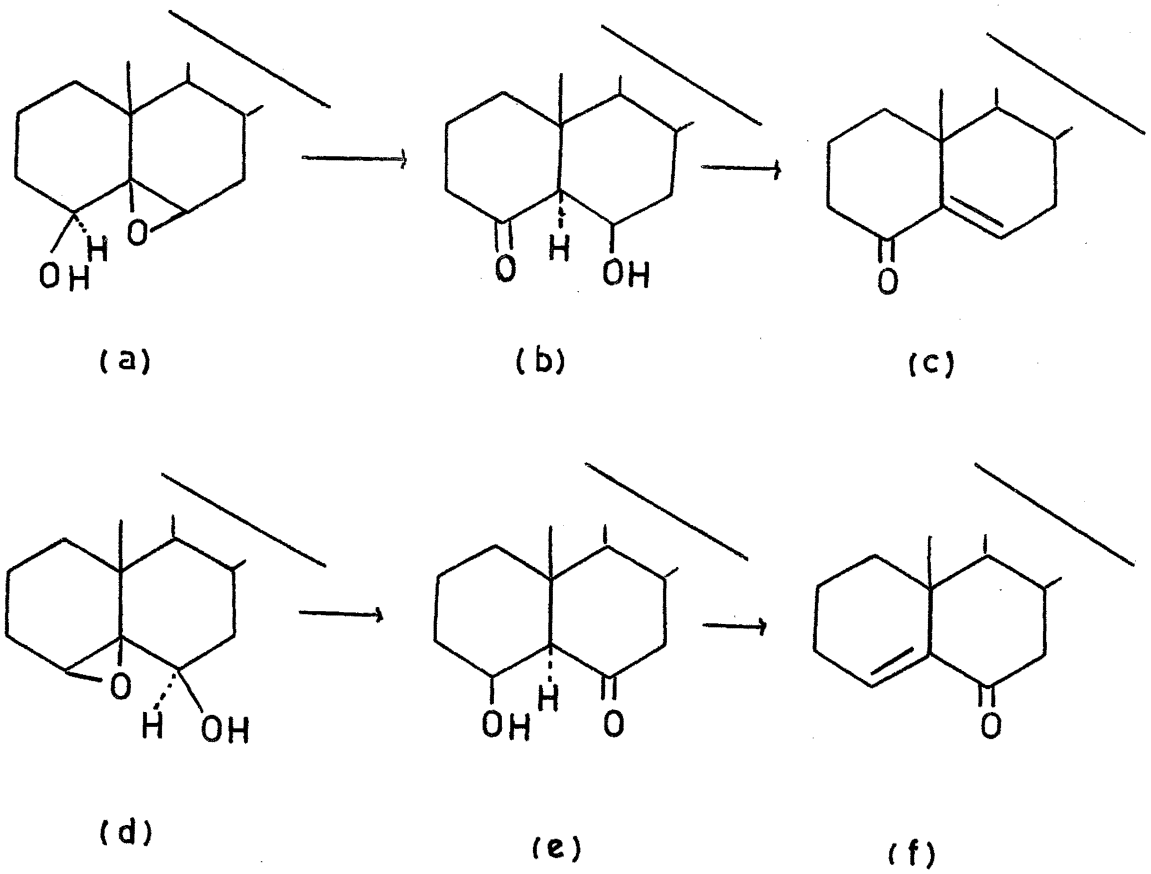



Fig. 27

starting material and pinocarvone (23). The formation of pinocarvone was confirmed by g.l.c. and examination of the IR spectrum.

2,10-Epoxy-10β-pinan-3β-ol (73) reacted under the same conditions to give complete conversion into pinocarvone. It is pertinent to note here that this compound was not detected in the product derived by the acid catalysed rearrangement of these epoxides (72 and 73); although amounts of pinocarvone of the order of 2% could have been detected.

A rate investigation of this system was carried out by studying the rate of appearance of pinocarvone as detected by its U.V. spectrum.

The reaction system was studied at 65° in from 0.06M to 0.5M solutions of sodium hydroxide in methanol-water (1:10). The reaction followed first order kinetics, allowing the 'pseudo first order' rate constants ($k_1$) to be found. The variation of the 'pseudo first order' rate constant ($k_1$), with hydroxyl ion concentration is shown in table 10. From the graph, fig. 29, it can be seen that the reaction is first order in hydroxyl ion, within experimental error. The second order rate constants ($k_2$) is given by the gradients of the graphs in fig.29. The rate constants for the reaction of 2,10-epoxy-10β-pinan-3α-ol (72) and 2,10-epoxy-10β-pinan-3β-ol

(73) with hydroxyl ion, eq. 2, are $3.0 \times 10^{-4}$ and $33 \times 10^{-4}$ mole$^{-1}$ sec$^{-1}$ respectively.

$$\text{rate} = k_2[\text{Epoxide}][OH^-] \qquad \underline{\text{Eq. 2}}$$

Table 10

| $[OH^-]$ moles.l$^{-1}$ | $k_1 \times 10^4$ sec$^{-1}$ | |
|---|---|---|
| | epoxide (72) | epoxide (73) |
| 0.0625 | | 1.2 |
| 0.125 | 0.57 | 3.6 |
| 0.250 | 0.97 | 6.5 |
| 0.500 | 1.7 | 15.2 |

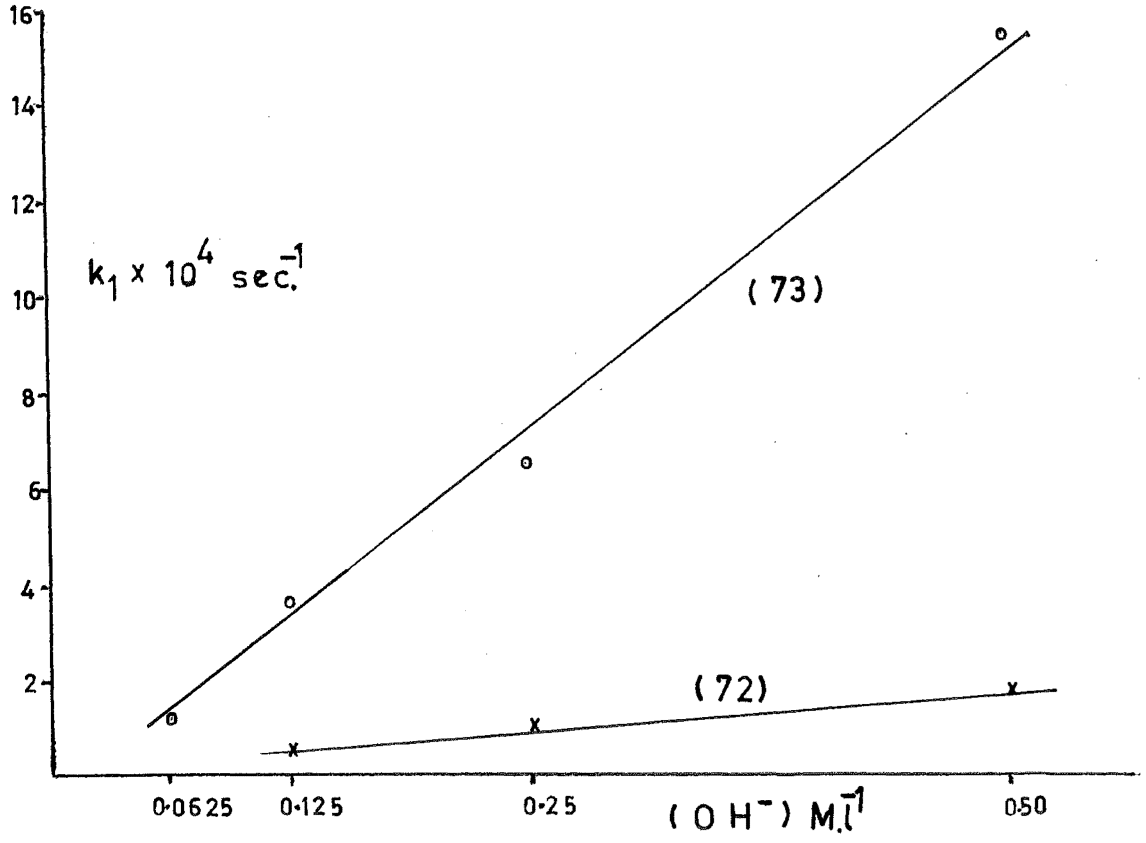



Fig. 29

Discussion: A reaction path involving acid opening of the epoxide ring concerted with a hydride shift is clearly not applicable in this case since the rearrangement occurs in a strongly alkaline medium.

In the case of 2,10-epoxy-10β-pinan-3β-ol the epoxide oxygen atom and the C3 hydrogen atom have a cis relationship, which excludes the possibility of a hydride shift concerted with C2-O bond cleavage.

The kinetic data above is consistent with a mechanism involving C3 proton abstraction by hydroxyl ion as the rate determining step. It is interesting to note that in the case of 2,10-epoxy-10β-pinan-3β-ol these processes are analogous to a base catalysed syn-elimination; whereas in the case of the epimeric epoxy alcohol (72) the steps correspond to a trans-elimination.

From a consideration of the expected preferred conformations of the two epoxy alcohols (72 and 73), fig. 30a and b, it can be seen that the 3β proton of the 3α-hydroxy epoxide (72), fig. 30a, is considerably more hindered than the corresponding 3α-proton of the 3β-hydroxy epoxide, fig. 3b.

The difference in accessibility of the C3 protons may account for the faster reaction rate (IIX) of 2,10-epoxy-10β-pinan-3β-ol as compared with

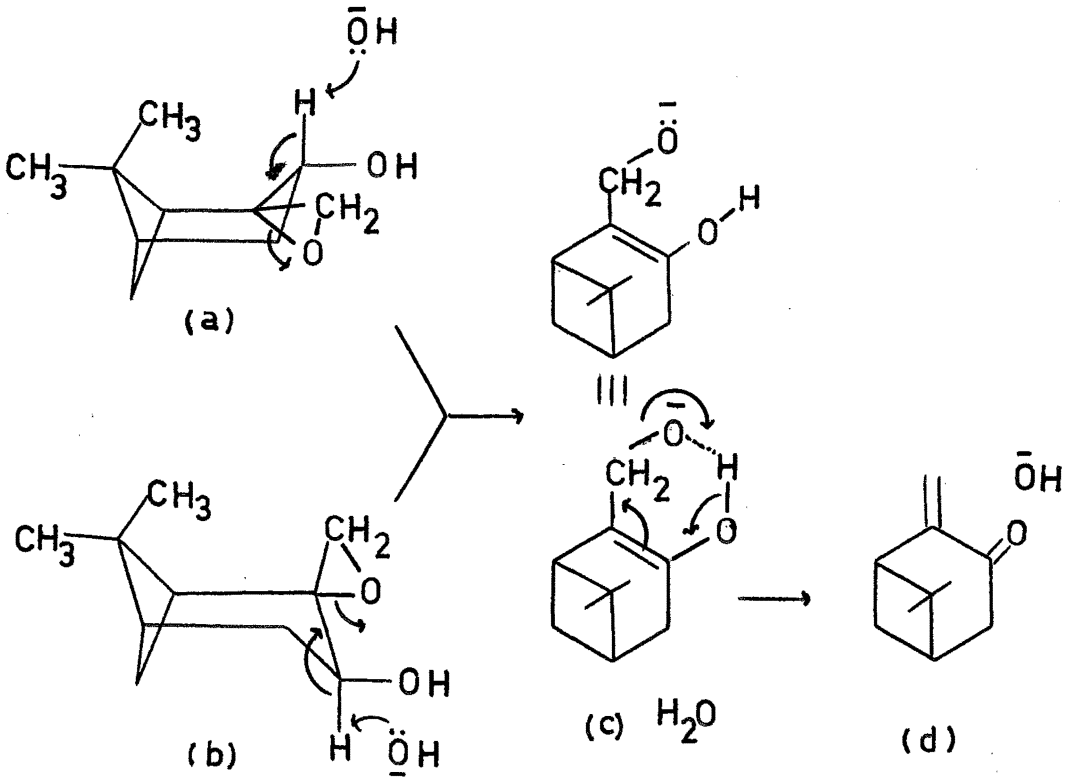



Fig. 30

2,10-epoxy-10β-pinan-3α-ol.

The subsequent step which is rapid, would involve an intra-molecular elimination of hydroxyl ion from the alkoxide, fig. 30c.

# APPENDIX C

## NMR analysis of pinanes

Throughout this thesis extensive use has been made of NMR spectra, to resolve the problems of structural assignment. Since a large number of NMR spectra of pinanes were obtained it was felt that sufficient spectra were now available, making use of those spectra which have been published, to attempt to correlate the variation in the chemical shift of the signal assigned to the C9 methyl protons.

Substituent effects on the methyl groups in the bornane and steroid series have already been published in some detail[106, 107]. The deshielding effect of a vicinal oxygen function was used in Chapter 1, Section 1, of this thesis to confirm the stereochemistry of 2-oxo-substituted pinanes at position C2. Table 11, selected from a more extensive one[107], illustrates the effect of a neighbouring hydroxyl group on the C19 methyl group of a 5α-steroid, fig.31.

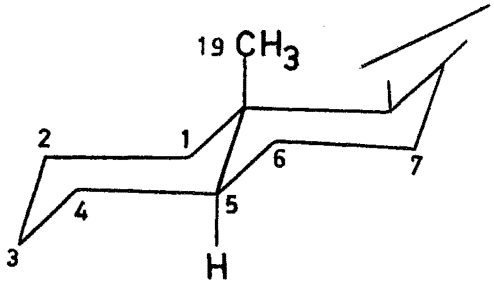



Fig. 31

Table 11

| Position of hydroxyl group | Type | ΔC19 ppm |
|---|---|---|
| 1α | anti-axial | 0.017 |
| 1β | equatorial | 0.050 |
| 2β | syn-axial | 0.250 |
| 3α | anti-axial | |
| 3β | equatorial | 0.037 |
| 4β | syn-axial | 0.267 |
| 6α | equatorial | -0.008 |
| 6β | syn-axial | 0.225 |
| 7α | anti-axial | -0.008 |
| 7β | equatorial | 0.025 |

From table 11 it can be seen that the effect of a syn-axial group is greater than the effect of an equatorial group which again is greater than the effect of an anti-axial group.

Table 12 incorporates most of the known NMR spectra of pinanes. The substituent effects on the C9 methyl protons, are shown relative to the value found for the parent compound.

Unless otherwise stated the spectra were of $CCl_4$ solutions.

Table 12

NMR Spectra of Pinanes

| | C3 | C8 | C9 | C10 | C9 |
|---|---|---|---|---|---|
| a. 10α-Pinanes | | | | | |
| 10α-pinane* | 1.20 | 0.84 | 0.87d | | 0.000 |
| 2-ol | 1.22 | 1.09 | 1.22 | | 0.25 |
| 10-ol | 1.24 | 0.86 | 3.27 d | | 0.02 |
| 3-one | 1.36 | 0.91 | 1.03d | | 0.07 |
| 10-al | 1.28 | 0.91 | 9.53d $J = 1.5$ cps | | 0.07 |
| 2,10-epoxy | 1.22 | 1.03 | 2.35q $\Delta\nu = 0.08$ ppm $J_{AB} = 5$ cps | | 0.19 |
| 2,10-epoxy-3-one | 1.37 | 1.03 | | | 0.19 |
| 2,10-diol | 1.26 | 1.09 | | | 0.25 |
| b. 10β-Pinanes | | | | | |
| 10β-pinane* | 1.20 | 1.02 | 1.01 d | | 0.00 |
| 2-ol | 1.24 | 0.95 | 1.24 | | -0.07 |
| 3α-ol* | 1.20 | 0.91 | 1.09d | | -0.11 |
| 3β-ol* | 1.18 | 1.06 | 1.07 | | 0.04 |
| 4α-ol" | 1.20 | 0.95 | | | -0.07 |
| 10-ol | 1.18 | 0.97 | 3.42 d | | -0.05 |
| 3-en-2-ol | 1.32 | 0.97 | 1.37 | | -0.05 |

| | C3 | C8 | C9 | C10 | ΔC9 |
|---|---|---|---|---|---|
| 3-one* | | 1.33 | 0.87 | 1.15d | -0.15 |
| 10-al | | 1.20 | 0.70 | 9.67 | -0.32 |
| 2,3α-epoxy | 2.90 | 1.27 | 0.93 | 1.27 | -0.09 |
| 2,10-epoxy | | 1.23 | 0.92 | 2.50q<br>$\Delta\nu = 0.17$<br>$J_{AB} = 5$cps | -0.10 |
| 2,10-epoxy-3α-ol | 3.79d<br>J = 5cps | 1.28 | 0.87 | 2.77<br>$\Delta\nu = 0.18$<br>$J_{AB} = 5$cps | -0.15 |
| 2,10-epoxy-3β-ol | | 1.27 | 0.92 | 2.82<br>$\Delta\nu = 0.83$<br>$J_{AB} = 5$cps | -0.10 |
| 2,10-epoxy-3-one | | 1.37 | 0.97 | | -0.05 |
| 2,3α-diol | | 1.23 | 0.93 | 1.26 | -0.09 |
| 2,3β-diol" | | 1.25 | 0.95 | 1.35 | -0.07 |
| 2,10-diol | | 1.26 | 0.93 | 3.38 | -0.09 |
| 2-ol-3-one | | 1.32 | 0.88 | 1.37 | -0.14 |
| 2,3α-diol carbonate | 4.50q<br>J = 8<br>J' = 2.5 cps | 1.35 | 0.88 | 1.53 | -0.14 |
| 2,10-diol carbonate" | | 1.26 | 0.83 | 4.12 | -0.19 |
| 2,3α-diol sulphite A | 4.90q<br>J = 7cps<br>J' = 2cps | 1.33 | 0.93 | 1.78 | -0.09 |
| 2,3α-diol sulphite B | 4.65<br>J = 8cps<br>J = 6 cps | 1.38 | 0.91 | 1.41 | -0.11 |

| | C3 | C8 | C9 | C10 | ΔC9 |
|---|---|---|---|---|---|
| 10-acetoxy-2-ol | | 1.24 | 0.92 | 4.00 | -0.10 |
| 10-tosyloxy-2-ol | | 1.17 | 0.77 | 3.83 | -0.25 |
| c. Pin-2-enes | | | | | |
| α-pinene* | | 1.27 | 0.84 | 1.65 | 0.00 |
| 10-ol | 5.38 | 1.28 | 0.83 | 3.85 | -0.01 |
| 4α-ol +" | 4.73 | 1.33 | 0.85 | 1.70 J = 1.5 cps | |
| 4-one +" | 4.45 | 1.45 | 0.98 | 1.97 | 0.14 |
| 10-ol +" | 3.36 | 1.32 | 0.73 | 0.29 | -0.11 |
| 3-acetoxy +" | 1.23 | 0.98 | 1.55 | | 0.14 |
| 10-bromo | 5.64 | 1.32 | 0.83 | | 0.01 |
| 10-methoxy | 5.42 | 1.28 | 0.83 | 3.19 | -0.01 |
| d. Pin-2,10-enes | | | | | |
| β-pinene* | | 1.23 | 0.72 | | 0.00 |
| 3-ene +" | | 1.35 | 0.88 | | 0.16 |
| 3α-ol | | 1.25 | 0.63 | 4.83 Δν = 0.20 ppm | -0.09 |
| 3β-ol | | 1.25 | 0.75 | 4.89d Δν = 0.67 ppm | 0.03 |
| 3-one | | 1.37 | 0.80 | 5.45 Δν = 0.92 ppm $J_{AB}$ = 2 cps | 0.06 |
| 3α-acetoxy °" | | 1.27 | 0.68 | 4.84 Δν = 0.18 ppm | -0.04 |

* Nakagawa et al [108]

\+ A.F.A. Wallis Ph.D. thesis

" $CDCl_3$ solution

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It should be noted that the pinane system differs from the bornane and steroid systems as the pinane skeleton is flexible. Conformational effects have been used throughout this thesis to explain reaction path. In particular a 3α-hydroxyl group is thought to favour an 'up' conformation whereas a 3β-group favours a 'down' conformation for 2,2-disubstituted pinanes. If the pinane system existed as a rigid 'down' conformer the effects of 3α- and 3β- hydroxyl groups on the chemical shift of the C9 methyl group should be similar to the effects of 3α and β hydroxyl groups on the C19 methyl group of the 5α- steroid series. The difference in chemical shift in this series is found to be 0.037 ppm, table 10. In the 10β-pinane series the difference is 0.15 ppm, table 11b, and in the pin-2,(10)-ene series it is 0.12 ppm. These chemical shift differences are clearly not consistent with a rigid 'down' conformation. Zweifel and Brown[16] have considered that 10β-pinan-3α-ol (12) and 10β-pinan-3β-ol (14) must both exist in a planar conformation to explain the similarity of the chemical

shift value of the C10 methyl groups (table 12b). In view of the complexity of the situation this assignment does not appear valid. In addition it seems unreasonable to expect a methyl group eclipsed with a hydroxyl group to have the same chemical shift as a methyl group eclipsed with a proton. The observed chemical shifts can be rationalised in terms of a 'down' conformation for the 3β-alcohol (14) and and 'up' conformation for the 3α-alcohol (12). The effect of the 3β-hydroxyl group on the C9 chemical shift (0.04 ppm) is similar to that found for an equatorial hydroxyl group in the steroid series, table 11. The unusually high deshielding effect of a 3α-hydroxyl group (-0.11) is consistent with a change in ring conformation to an 'up' conformation.

The chemical shifts of the C9 methyl group in the 3-keto compounds (48 and 83) are also of interest. In the 10β-ketone a shielding effect (-0.15ppm) is observed whereas in the 10α-ketone the effect is deshielding (0.07 ppm). Consequently 10α-pinan-3-one must exist as the down conformer, fig. 32a, and 10β-pinan-3-one as the 'up' conformer, fig. 32b. These conformations are consistent with minimum non-bonded interactions.

Attempts to correlate the C9 shifts with chemical structure involves difficulties due to the effects

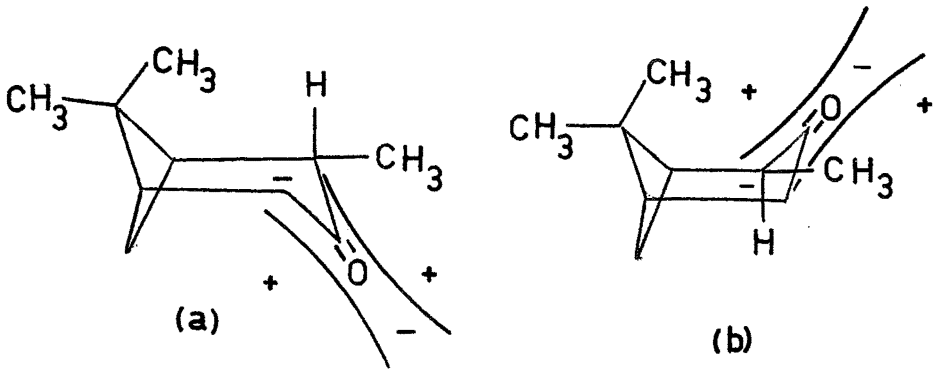


Fig. 32

of conformational changes. It is possible, however, to establish the structural configuration of a substituted pinane with some degree of certainty from these shifts.

The stereochemistry of 1-oxo-substituted compounds has been rigorously established by means of this C9 shift, see Section 1. This has been possible in this particular instance since the chemical shift difference between the two configurations is large.

The stereochemistry at C3 presents more difficulty because of the conformational effects discussed above. It is possible, however, to distinguish between 3-hydroxy epimers in the 10β series since the C9 methyl group of a 3β-hydroxy epimer will be less shielded than the C9 methyl group of a 3α- epimer. A 3α-hydroxy epimer can have the

hydroxyl group in conformations corresponding to anti-axial to equatorial, i.e. only weak interaction; whereas in the 3β- epimer conformations can vary from syn-axial in an 'up' conformation to equatorial in a 'down' conformation. Additionally it appears that effects of ring conformation on the C9 methyl proton shift operates in such a direction that the shielding effect of a 3α-hydroxyl group relative to a 3β-hydroxyl group is enhanced.

Although it is possible to draw some conclusions about ring conformation from the chemical shifts more accurate results are obtained from the consideration of the relationship between the dihedral bond angle (φ) and coupling constant (J) for the ring methylene protons. The spectra are generally too complex to obtain J values; but in those cases where a C3 proton is sufficiently deshielded to be observed separately, and where there is no proton substitution on the C2 atom, J values can be obtained. Where possible the conformation has been derived from these J values. Unfortunately in many cases the signal peaks observed are too broad to determine the J values. The effect of a 3-hydroxyl group on ring conformation is illustrated by the results in table 13.

Table 13

| | observed J values (cps) | ($\Phi^{o}$) | con-formation |
|---|---|---|---|
| 10β-pinan-2,3α-diol | 5.5, 9 | 35, 148 | 'up' |
| 2,10-epoxy-10β-pinan-3β-ol | 9.5, 7 | 21, 152 | 'down' |

# EXPERIMENTAL

Specific rotation measurements were carried out on chloroform solutions in a 10 cm. tube. Infrared spectra were recorded on Perkin-Elmer 337, 137 and 221 spectrometers, and are on liquid film unless otherwise stated. Ultraviolet spectra were recorded on a Beckman DB-G spectrometer on methanol solutions.

NMR spectra were obtained on a Varian A60 with spin decoupling and time averaging computer attachments. The spectra were of carbon tetrachloride solutions with TMS and chloroform as internal standards unless otherwise stated.

Gas chromatography was carried out using a Beckman Megachrom with 25% polyethylene glycol monostearate on firebrick columns, for large scale purification of α- and β-pinene. For small scale preparative work a Micro Tek 2500 IIR with exit splitter and flame ionisation detector was used. Columns were $\frac{1}{4}$" aluminium packed with 20% carbowax 20M and 20% S.E. 30 on 30 - 80 celite. Samples were trapped in carbon tetrachloride solution. For analytical work a Micro Tek 2500 IIR and Aerograph 204 were used, columns were $\frac{1}{4}$" and $\frac{1}{8}$" respectively, packed with 3% carbowax 20M, S.E. 30

or Apiezon L on Chromosorb G, non acid washed and treated with HMDS.

Fractional distillations were carried out using Nester-Faust annular teflon and spinning band columns.

Alumina (P.Spence, grade H) was used in column chromatography.

Temperature readings are not corrected. Literature values for physical constants are those quoted in Elsevier, "Encyclopaedia of Organic Chemistry", series III, vol. 12A, unless otherwise stated.

Perbenzoic acid:

Perbenzoic acid was made by the action of 70% hydrogen peroxide on benzoic acid[109]. 70% hydrogen peroxide was made by concentration of a 50% solution by distillation at 10 mm and 60° till the residue had a density of 1.30. (lit.cit. for 70% hydrogen peroxide d = 1.30[110]).

2,10-Epoxy-10β-pinane (21):

To an ice cold solution of β-pinene (43g; purified by prep. g.l.c.) in diethyl ether (1l) a solution of perbenzoic acid (54g by titration) in benzene (500 ml) was added.

The reaction mixture was left for 48 hr at 0°. The solution was then extracted with aqueous sodium hydroxide (1M), till the acidified washings gave no reaction with starch-iodide paper. The organic layer was then dried with anhydrous sodium sulphate and the solvent removed.

The residue was distilled through a short Vigreux column to give epoxide material (31.9g; 66% theoretical yield), b.p.$_{12}$ = 83 - 85°, $n_D^{21}$ = 1.4753 (lit.cit. $n_D^{21}$ = 1.4758), $\delta_{CCl_4}$ = 0.92 (3H), 1.23(3H) and 2.35q (2H; $J_{AB}$ = 5 cps, $\Delta\nu$ = 0.17 ppm). The NMR spectrum indicated 92.5% 2,10-epoxy-10β-pinane and 7.5% 2,10-epoxy-10α-pinane (22).

10β-pinan-2-ol (8):

To a suspension of lithium aluminium hydride (1g) in diethyl ether (150 ml) was added 2,10-epoxy-10β-pinane (1g). The suspension was heated under reflux for 8 hours. After careful decomposition of the excess lithium aluminium hydride with aqueous sodium hydroxide (6M) the product 10β-pinan-2-ol (0.92g; 91% theoretical yield) was isolated. $\delta_{CCl_4}$ = 0.95(3H), 1.24(6H) m.p. = 75° (lit.cit. 79°), g.l.c. on carbowax 20M at 110° indicated less than 0.5% 10α-pinan-2-ol.

Norpinone (62)

β-Pinene (20g) was dissolved in absolute methanol (180 ml) in a 250 ml flask fitted with a bubbler tube and the reaction vessel kept at ca. -70°.

Ozone in oxygen generated by a silent discharge apparatus was passed through the solution until the effluent gas gave a strong colouration with moist starch-iodide paper (ca. 24 hr). The solution was poured into water (1l) and left for 24 hr.

Extraction with diethyl ether (3 x 100 ml) and subsequent washing with water, until the washings no longer coloured starch-iodide paper, gave, after evaporation, and fractional distillation nopinone (13g; 66% theoretical yield), $b.p._{16} = 92.5 - 93$, $\nu_{max}$ at 2890, 1720, 1450, 1195 and 1028 $cm^{-1}$, $\delta_{CCl_4} = 0.85$ (3H), 1.35 (3H).

2,10-Epoxy-10α-pinane (22):

Sodium hydride (24g, 50% dispersion in oil) was washed with pentane to remove paraffin oil, and then added to dry dimethyl sulphoxide (250 ml) at 65-70°. The mixture was stirred vigorously under nitrogen. To this mixture tetrahydrofuran (100 ml) was added and the mixture cooled to -10°. Keeping

the temperature below 0°, trimethyl sulphonium iodide (125 g) was added, followed by nopinone (35.5g). The solution was stirred for 2 hr at 10°. Water (500 ml) was added and the epoxide extracted with pentane (1l.). Evaporation of the solvent and distillation of the resulting product gave 2,10-epoxy-10α-pinane (32.9g; 84% of theoretical yield) m.p. = 18.5° $[\alpha]_D^{20}$ = +38° (c = 1.1), Found: C, 78.9; H, 10.4. $C_{10}H_{16}O$ requires C, 78.9; H, 10.6%. $\delta_{CCl_4}$ = 1.03(3H), 1.22 (3H) and 2.35q(2H, $J_{AB}$ = 5 cps, $\Delta\nu$= 0.08 ppm). $\nu_{max}$ at 2930, 1470, 1400, 935 and 909 $cm^{-1}$.

10α-Pinan-2-ol (7):

Nopinone (0.7g) was added to a refluxing solution of methylmagnesium iodide (prepared by the reaction of magnesium (1g) with methyl iodide (3 ml) in ether) in 200 ml dry ether. The reaction mixture was refluxed for 2 hr. Isolation of the terpene material via ether gave 10α-pinan-2-ol (0.65g; 83% theoretical yield), m.p. = 56 - 57° (lit.cit. 58-59°) $\delta_{CCl_4}$ = 1.09 (3H), 1.22(6H).

Reduction of 2,10-epoxy-10α-pinane:

To a solution of 2,10-epoxy-10α-pinane (2g) in

diethyl ether (75 m.) was added lithium aluminium hydride (2g) and the resulting suspension heated under reflux for 2 hr. Isolation *via* ether and sublimation of the product gave 10α-pinan-2β-ol (1.4g; 63% theoretical yield), m.p. 58° NMR, IR and g.l.c. retention on carbowax and SE30 column identical to product obtained from nopinone above. (No 10β-pinan-2-ol could be detected by G.C. analysis.)

10β-Pinane-2,10-diol (63):

A solution of potassium permanganate (100g) and magnesium sulphate (75g) in 2l. of water was dropped into a stirred solution of β-pinene (100g) in 1.5 l. of ethanol. The temperature was kept below 5° by immersion in an ice-salt bath. After 2 hr the mixture was filtered through celite "filter-aid" on a Buchner funnel. The filtrate was reduced in volume by distillation until the vapour reached a temperature of 99°.

Salt was added to the residue and the glycol extracted with dichloromethane (2 x 250 ml). After removal of solvent the product was adsorbed onto alumina (200g). Elution with ether and recrystallisation from pentane gave 10β-pinane-2,10-

diol (8.4g; 6.7% theoretical yield) m.p. = 83.5° (lit.cit. 75-77°), $\delta_{CCl_4}$ = 0.93 (3H), 1.26 (3H) and 3.38 (2H), $\nu_{max}$ at 3280, 2900, 1465, 1388, 1368, 1235, 1218, 1059 and 1033 $cm^{-1}$ ($CHCl_3$ soln.).

In a repeat reaction the crude glycol was purified by fractional distillation with a 4" Vigreux column to give 10β-pinane-2,10-diol (19.3g; 15.5% theoretical yield) $b.p._2$ = 105-120°, m.p. = 70-75°, NMR indicated 97% pure glycol.

Oxidation of β-pinene with osmic acid:

To a solution of β-pinene (8.3g) osmic acid (0.04g) and ether (100 ml) was added to a solution of $H_2O_2$ (3.5M, 100 ml) in anhydrous ether (prepared by adding 35% aqueous hydrogen peroxide to ether and drying with anhyd. sodium sulphate).

After an induction period of 6 hr a violent reaction occurred. The reaction mixture was washed with ferrous sulphate solution and the organic phase dried over sodium sulphate. After removal of solvents the residue was adsorbed onto deactivated alumina (50g). Elution with pentane gave nopinone (1.8g). Further elution with 20% ether in pentane gave 10β-pinane-2,10-diol (1.48g), m.p. = 82°. IR and NMR identical to those of sample above.

10-Tosyloxy-10β-pinan-2-ol (65):

A solution of 10β-pinane-2,10-diol (2g) and p-toluene sulphonyl chloride (2.5g) in pyridine (2.5 ml) was kept at 60° for 2 hr. The reaction mixture was poured into ice-water and the product extracted with ether to give 10-tosyloxy-10β-pinan-2-ol (2.7g; gum). $\delta_{CCl_4}$ = 0.77 (3H), 1.17 (3H), 2.44 (4H), 3.83 (2H) and 7.52q (4H; $J_{AB}$ = 8 cps $\Delta\nu$ = 0.43 ppm). Addition of $D_2O$ reduced the integral at δ = 2.44 to 3H.

Reduction of 10-tosyloxy-10β-pinan-2-ol:

To a solution of 10-tosyloxy-10β-pinan-2-ol (1g) in ether (50 ml) was added lithium aluminium hydride (1g) and the suspension heated under reflux for 2 hr. Isolation of terpene material via ether extraction and sublimation gave 10β-pinan-2-ol (0.37g; 76% theoretical yield), m.p. = 76°. NMR, IR and retention on polar and non-polar g.l.c. columns identical with sample prepared by reduction of 2,10-epoxy-10β-pinane above.

10β-pinane-2,10-diol cyclic sulphite (66):

To a solution of 10β-pinane-2,10-diol (1g) and pyridine (1ml) at 0° was added thionyl chloride

(0.5ml). Addition of water followed by extraction with pentane (2 x 10 ml) and removal of solvent gave 10β-pinane-2,10-diol cyclic sulphite (0.54 g), m.p. = 78 - 80°d, (Found C, 56.1; H, 7.8; S, 14.2. $C_{10}H_{16}O_3S$ requires C, 55.5; H, 7.4; S, 14.8%). $\delta_{CCl_4}$ = 0.89 (3H), 1.31 (3H) and 4.28q (2H; $J_{AB}$ = 9 cps, $\Delta\nu$ = 0.1 ppm). $\nu_{max}$ at 1202 $cm^{-1}$ (Nujol mull).

10β-pinane-2,10-diol cyclic carbonate (67):

Sodium (0.02 g) was dissolved in diethyl carbonate (4 g) in a 25 ml flask fitted with a short Vigreux column. 10β-Pinane-2,10-diol (5 g) was added and the flask heated till no more ethanol distilled off. A crystalline residue (5.7 g) was left in the flask (carbonate and starting material, by NMR). Recrystallisation from chloroform gave 10β-pinane-2,10-diol cyclic carbonate (2.2 g), m.p. = 141 - 142°, $\delta_{CDCl_3}$ = 0.83 (3H), 1.26 (3H) and 4.12 (2H). $\nu_{max}$ at 1795 $cm^{-1}$ (nujol mull). (Found C, 67.3; H, 8.2. $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.2).

10β-pinane-2,3α-diol (27)

A solution of potassium permanganate (100 g) and magnesium sulphate (75) in water (2 l) was added at 0 - 5° to a stirred solution of α-pinene (100 g; $[\alpha]_D^{20}$ = + 4°) in ethanol (1.5 l). After 2 hr the mixture was filtered through celite "filter-aid" on a Buchner funnel. The filtrate was reduced in volume by distillation till the temperature of the vapour reached 99°. Addition of salt followed by extraction with dichloromethane (2 x 250 ml) and evaporation afforded crude glycol. Fractional distillation with a spinning band column gave α-pinene (13.4 g), $b.p._5$ = 29°; pinonic acid (23.4 g), $b.p._5$ = 113 - 114, m.p. = 105° (after recrystallisation; lit. cit. m.p. = 103°) and 10β-pinane-2,3α-diol (14 g), $b.p._5$ = 125 - 126°, m.p. = 38 - 40° (lit. cit. m.p. 56 - 57° for material from α-pinene $[\alpha]_D$ = +38.5). (The mother liquor from recrystallisation of the pinonic acid fraction was shown by NMR to contain 10β-pin-3-one-2-ol).

10β-Pinan-3-one-2-ol (25)

Powdered potassium permanganate (272 g) was added to an ice cold solution of α-pinene (136 g; $[\alpha]_D^{20}$ = - 37°) in acetone (1080 ml) and water (120 ml)

during 8 hrs at 0 to 5°.

The manganese dioxide was filtered off with a celite "filter-aid" filter and the acetone removed by distillation. The terpene material was isolated *via* ether. Fractional distillation gave 10β-pinan-3-one-2-ol (45 g; 27% theoretical yield), m.p. = 30° (lit. cit. 34.5 - 35.5), $n_D^{20}$ = 1.4890 (supercooled liquid; lit. cit. $n_D^{20}$ = 1.490), $[\alpha]_D^{20}$ = +36° (C = 0.9) (lit. cit. $[\alpha]_D^{20}$ = - 41.2°, from α-pinene $[\alpha]_D^{20}$ = +38°). $\delta_{CCl_4}$ = 0.88 (3H), 1.32 (3H) and 1.37 (3H).

Meerwein-Ponndorf-Verley reduction of 10β-pinan-3-one-2-ol

10β-pinan-3-one-2-ol (15 g) was treated with aluminium isopropoxide (15 g) and absolute isopropanol (15 ml) in a 50 ml flask attached to a spinning band distillation column.

Acetone-isopropanol was taken off and replaced with isopropanol until the distillate contained no acetone (by g.l.c.).

The isopropanol was removed by distillation and the residue stirred with aqueous alkali for 1 hr. Isolation of product *via* ether gave an oil (14.6 g) shown by g.l.c. to be a mixture of three compounds

in the ratio 7:6:87 in order of elution.

The three compounds were isolated by fractional distillation and shown to be 10α-pinan-3-one (48; NMR and IR spectra identical to those of an authentic sample), starting material and 10β-pinane-2,3 -diol (9.2 g), m.p. = 44 - 48°, $[\alpha]_D^{20}$ = 2° (lit. cit.[45] m.p. = 56° after purification *via* urethane; $[\alpha]_D^{20}$ = 3.3, from α-pinene $[\alpha]_D^{20}$ = +38°). NMR and IR spectra were identical to those of the diol prepared by hydroxylation of α-pinene with aqueous permanganate above.

Lithium aluminium hydride reduction of 10β-pinan-3-one-2-ol

10β-Pinan-3-one-2-ol (3.3 g) in dry ether (10 ml) was dropped into a refluxing suspension of lithium aluminium hydride (1 g) in ether (50 ml). The mixture was heated under reflux for 2 hrs. Excess lithium aluminium hydride was removed by careful addition of aqueous sodium hydroxide (6M). Isolation of product via ether and recrystallisation from ether gave 10β-pinane-2,3β-diol (26; 1.3 g, m.p. = 150 - 153° (lit. cit. m.p. = 155 - 160°) $\delta_{CDCl_3}$ = 0.95 (3H), 1.25 (3H) and 1.35 (3H).

10β-Pinane-2,3α-diol cyclic sulphites (68 and 69)

To a solution of 10β-pinane-2,3α-diol (10 g) and pyridine (10 ml) in ether (500 ml) thionyl chloride (5 ml) was added at 0°. Water was added and the suspension extracted with pentane (2 x 100 ml). Evaporation of the solvent gave a crystalline product (8.68 g), m.p. = 60 - 64° (Found: C, 55.9; H, 7.4. $C_{10}H_{16}O_3S$ requires C, 55.5; H, 7.5). The NMR spectrum indicated this to be a mixture of two isomers.

The two isomers were isolated by fractional recrystallisation from pentane. Isomer A (68) m.p. = 50 - 52°, $\nu_{max}$ at 1210 $cm^{-1}$ (nujol mull). (Found: C, 55.2; H, 7.1, S 14.4%). $\delta_{CCl_4}$ = 0.93 (3H), 1.33 (3H), 1.78 (3H) and 4.90q (1H; J = 7, J' = 2 c.p.s.). Isomer B (69) m.p. = 102° $\nu_{max}$ at 1200 $cm^{-1}$ (nujol mull). (Found: C, 55.6; H, 7.4). $\delta_{CCl_4}$ = 0.91 (3H), 1.41 (6H) and 4.65q (1H; J = 8, J' = 6 c.p.s.).

Hydrolysis of 10β-pinane-2,3α-diol cyclic sulphite mixture

The sulphite mixture (68 and 69; 0.5 g) from the preparation above was treated with sodium hydroxide (0.5 g) in methanol-water (1:1; 10 ml)

on a steam bath for 1 hr. Isolation of terpene material *via* ether gave 10β-pinane-2,3α-diol (0.30 g).

NMR and IR spectra were identical to those of an authentic sample.

10β-pinane-2,3α-diol cyclic carbonate (70)

Pyridine (15 ml) was added to a solution of 10β-pinane-2,3α-diol in ethyl chloroformate (15 ml) in a flask fitted with a refluxing condenser. An exothermic reaction took place. Ether (20 ml) was added, and the organic layer was washed with water to remove pyridine hydrochloride. Removal of the solvent and distillation through a short Vigreux column gave pyridine, ethyl chloroformate, diethyl carbonate and 10β-pinane-2,3α-diol cyclic carbonate (2.7 g), b.p.$_{11}$ = ca. 140, m.p. 80 - 82°, $[\alpha]_D^{20}$ = - 31° (C = 1.1), $\nu_{max}$ at 1715, 1750 and 1815 $cm^{-1}$ (Found: C, 67.8; H, 8.1. $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.2). $\delta_{CC;4}$ = 0.88 (3H), 1.35 (3H), 1.53 (3H) and 4.50q (1H; J = 8, J' = 6 c.p.s.).

trans-Pinocarveol (20)

a) Hydrogen peroxide (100 ml, 35%) was carefully added to a solution of selenium dioxide (3.5 g) in

β-pinene (100 g; 87.4% β, 9.6% α and 3% dipentene) and tert.-butanol (140 ml) at such a rate that the temperature did not exceed 40°. Water (200 ml) was added and the product extracted with ether (2 x 250 ml). The ether layer was washed with aqueous sodium hydroxide (1M; 100 ml) and saturated ammonium sulphate solution (4 x 100 ml).

After removal of solvent the crude product was shown by g.l.c. to consist of α- and β-pinene, dipentene and trans-pinocarveol.

Fractional distillation with a 12" glass helix column gave β-pinene (15 g) and trans-pinocarveol (47 g) $b.p._2 = 60°$, $n_D^{21} = 1.4987$, $[\alpha]_D^{20} = +60°$ (C = 1.0) (lit. cit. $n_D^{21} = 1.4992$, $[\alpha]_D^{20} = +59°$). $\delta_{CCl_4} = 0.63$ (3H), 1.25 (3H), 4.83q ($\Delta\nu = 0.20$ p.p.m. J = 1 c.p.s.).

b) Lead tetracetate (300 g) was added to a solution of β-pinene (136 g) in dry benzene (1.5 l). The temperature was maintained at 60 - 65° during the addition by means of an ice bath. The precipitate of lead acetate was filtered off and washed with benzene (2 x 100 ml). Removal of solvent from the combined filtrates gave an oil (150 g).

Distillation gave β-pinene (45 g) $b.p._{15}$ = 50 - 70°, monoacetates (51 g) $b.p._{15}$ = 90 - 120°

and residue (45 g). The monoacetate fraction was treated with potassium hydroxide (60 g) in methanol (150 ml) and water (9 ml) for 1 hr. Isolation of terpene material *via* ether gave crude alcohol (40 g).

Fractional distillation (annular spinning band) gave *trans*- pinocarveol (20 g) $b.p._{3.5} = 72 - 80^{\circ}$ (IR and NMR were identical to sample above) and pin-2-en-10-ol (50; 3g) $b.p._{3.5} = 80 - 87^{\circ}$ $\delta_{CCl_4}$ = 0.83 (3H), 1.28 (3H), 3.85 (2H) and 5.38 (1H).

*Pinocarvone* (23)

Selenium dioxide (144 g) was added to a refluxing solution of β-pinene (180 g) in carbontetrachloride (270 ml). Refluxing was continued for a further 10 hrs, the liquid was then decanted and the residue extracted with ether ( 2 x 100 ml). The combined liquid layers were reduced in volume to 200 ml by distillation. Steam distillation followed by fractional distillation gave pinocarvone (14.3 g), $[\alpha]_D^{20} = +60$ (C = 0.9) $n_D^{20} = 1.4943$ (lit. cit. $[\alpha]_D^{20} = +63^{\circ}\ 37'$ $n_D^{20} = 1.4947$).

b) *trans*-Pinocarveol (35 g) was stirred with active manganese dioxide (350 g; prepared by reacting together manganous sulphate and potassium permanganate in alkaline solution[111]) in pentane (1.5 l) for 24

hrs. The manganese dioxide was filtered off with a celite "filter-Aid" filter and washed with ether (2 x 200 ml). Evaporation of the solvent gave pinocarvone (31 g) $[\alpha]_D^{20}$ =+60° (C = 1.0). NMR and IR spectra were identical to those of the sample above.

cis-Pinocarveol (56)

a) Bromine (22.5g) in acetic acid (40 ml) was added dropwise to a stirred solution of pinocarvone (23; 20 g) in ether (100 ml) at 0° to 5°. The addition of bromine solution was stopped at the first sign of colouration of the reaction mixture. Isolation via ether gave a gum, which was redissolved in acetic acid (400 ml) and water (50 ml). The reaction vessel was immersed in an ice-bath, and zinc powder (90 g) was added at such a rate that the temperature did not exceed 10°. The acetic acid was neutralised with an excess of sodium hydroxide solution (6M). Isolation via ether gave an oil which was fractionally distilled to give cis-pinocarveol (11.1 g) b.p.$_5$ = 80°, m.p. = 50° $[\alpha]_D^{20}$ = -40 (C 0.9), $\delta_{CCl_4}$ = 0.73 (3H), 1.25 (3H) and 4.89d (2H, $\Delta\nu$ = 0.67 ppm). (lit. cit. m.p. = 51°).

b) Aluminium isopropoxide (40 g) was dissolved in

absolute isopropanol (40 ml, dried with magnesium) and pinocarvone (36.7 g) added.

The reaction vessel was attached to a spinning band distillation column. Acetone-isopropanol was distilled off and replaced with pure isopropanol until the stillhead temperature reached 82° (ca. 6 hrs). The isopropanol was distilled off and sodium hydroxide solution (50 ml; 6M) added to the residue. Isolation *via* ether gave an oil (36 g) which was fractionally distilled to give starting material (10 g) and *cis*-pinocarveol (13.1 g) m.p. = 49 - 50°. NMR and IR spectra were identical to those of the sample above.

2,10-epoxy-10β-pinan-3α-ol (72)

*trans*-Pinocarveol (20 g) was added to an ice cold solution of perbenzoic acid (72 g, by titration) in ether (1 l.). The solution was kept at 7° for three days. The reaction mixture was then washed with dilute alkali until the acidified washings gave no reaction with starch-iodide paper. Evaporation followed by distillation at 1 mm through a short Vigreoux column gave 2,10-epoxy-10β-pinan-3α-ol (14 g); 63% of theoretical yield), $b.p._1$ = 70 - 72°, m.p. 12 - 15°, $[\alpha]_D^{20}$ = +44 (C = 0.9). (Found: C, 71.6; H, 9.5, $C_{10}H_{16}O_2$ requires C, 71.4; H, 9.6%).

Reduction of 2,10-epoxy-10β-pinan-3α-ol:

To a solution of 2,10-epoxy-10β-pinan-3α-ol (0.75 g) in ether was added lithium aluminium hydride (0.5 g), and the solution was heated under reflux for 4 hrs. The reaction was stopped by the addition of aqueous sodium hydroxide (6N) and the alumina produced dissolved in an excess of aqueous sodium hydroxide (50 ml; 1M). Isolation of terpene material *via* ether gave 10β-pinane-2,3α-diol (27; gum); shown to be identical to an authentic sample by NMR and g.l.c.

2,10-Epoxy-10β-pinan-3β-ol (73):

*cis*-Pinocarveol (56; 1 g) was added to an ice cold solution of perbenzoic acid (24 g, by titration) in ether (250 ml) and benzene (150 ml). The reaction mixture was kept at 8° for 48 hrs. The organic layer was then washed with aqueous sodium hydroxide (1M) until the acidified washings gave no colouration with starch-iodide paper. Evaporation of the solvent gave 2,10-epoxy-10β-pinan-3β-ol (11.3 g). *Distillation of the crude epoxide gave pure epoxide (5.0 g),

* Distillation is not recommended since in several instances the compound decomposed during attempted distillation. The epoxide is essentially pure before distillation.

b.p.$_{0.5}$ = 90°, m.p. = 6°, $[\alpha]_D^{20}$ = -30 (Found: C, 71.5; H, 9.4. $C_{10}H_{16}O_2$ requires: C, 71.4; H, 9.6%) $\delta_{CCl_4}$ = 0.92 (3H), 1.27 (3H) and 2.82q (2H; $\Delta\nu$ = 0.83 ppm, $J_{AB}$ = 5 c.p.s.).

Reduction of 2,10-epoxy-10β-pinan-3β-ol:

Lithium aluminium hydride (0.5 g) was suspended in dry ether (50 ml) and a solution of 2,10-epoxy-10β-pinan-3β-ol (0.5 g) in dry ether (10 ml added). After refluxing for 1 hr the excess lithium aluminium hydride was removed by the careful addition of aqueous sodium hydroxide (6M).

Isolation via ether gave 10β-pinane-2,3 -diol (26; 0.45 g) m.p. 152 - 153° (lit. cit. 155 - 160°) identical to the product produced by lithium aluminium hydride reduction of 10β-pinan-3-on-2-ol (by NMR and IR).

2,10-epoxypinan-3-ones (74 and 75):

Sodium hydroxide (2 g) in water (8 ml) was dropped into a solution of pinocarvone (15 g) in methanol (100 ml) and hydrogen peroxide (34 g, 130 vol) at 15°. The temperature did not exceed 25°C during the addition. After 4 hours the reaction

mixture was poured into water and extracted with dichloromethane (3 x 200 ml). Evaporation followed by distillation through a short Vigreux column gave an oil (14.1 g; 85% theoretical yield), b.p.$_{1}$ = 90°, $n_D^{15}$ = 1.4905, $[\alpha]_D^{20}$ = +58. (lit. cit.[38]: $n_D^{20}$ = 1.4889; $[\alpha]_D^{20}$ = -64°, from (-) pinocarvone). The NMR spectrum ($\delta_{CCl_4}$ = 0.97, 1.03, 1.37 and 1.38) indicated that two isomers were present (74 and 75) in the ratio 7:3.

Reduction of the 2,10-epoxypinan-3-one mixture:

A solution of 2,10-epoxypinan-3-one (1 g) in dry ether (10 ml) was dropped into a solution of lithium aluminium hydride (0.5 g) in dry ether (50 ml) and the reaction mixture was refluxed for 2 hrs. The reaction was then stopped by the addition of a saturated solution of sodium hydroxide in water. Isolation of terpene material via ether gave a gum (0.73 g). NMR and g.l.c. indicated a complex mixture of diols containing ca. 30% 10β-pinane-2,3α-diol (27).

Oxidation of 2,10-epoxy-10β-pinan-3α-ol:

2,10-Epoxy-10β-pinan-3α-ol (1 g) in pyridine (10 ml) was added to a suspension of chromium trioxide (1 g) in pyridine (10 ml) and left for 6

hours at room temperature. Extraction with pentane gave an oil (0.7 g), shown by NMR to consist of starting material and 2,10-epoxy-10β-pinan-3-one (74), $\delta_{CCl_4}$ = 0.97 (3H) and 1.38 (3H) (by difference) identical to the major compound from the reaction of alkaline hydrogen peroxide with pinocarvone above (by NMR).

10β-pinan-10-ol (86):

A solution of sodium borohydride (3.8 g) in diglyme (80 ml) was dropped into a vigorously stirred solution of boron trifluoride etherate (33.7 ml) in diglyme (80 ml). The diborane so formed was carried by a slow stream of nitrogen into an ice-cold solution of β-pinene (27.2 g) in tetrahydrofuran (60 ml) during 2 hrs.

The solution of alkyl borane was divided into two equal portions. To one half of the borane was added sodium hydroxide solution (3M; 22.5 ml) and hydrogen peroxide (100 vol, 12.5 g) was dropped in over a period of 30 min.

Isolation of terpene material *via* ether and distillation from a 25 ml flask with a Vigreux side arm gave 10β-pinan-10-ol (12 g). $\delta_{CCl_4}$ = 0.97 (3H), 1.18 (3H) and 3.42 (2H). (lit. cit.[16] $\delta_{CCl_4}$ = 0.97 and 1.18).

10α-pinan-10-ol (87):

Solvent was distilled off the second alkyl borane fraction above till the temperature reached 140°. The solution was then refluxed at this temperature for 2 hrs. Isolation *via* ether and distillation as above gave 10α-pinan-10-ol (8.4 g), $\delta_{CCl_4}$ = 0.86 (3H), 1.24 (3H) and 3.27 (2H). (lit. cit.[16] $\delta_{CCl_4}$ = 0.82 and 1.20).

Oxidation of 10β-pinan-10-ol:

Chromium trioxide (3 g) was added slowly to pyridine (30 ml) taking care that the temperature did not exceed 20°. To this suspension was added a solution of 10β-pinan-10-ol (1 g) in pyridine. After 12 hrs the suspension was poured into water (250 ml) and extracted with pentane-ether (1:1). The organic layer was washed several times with water, dried and the solvents evaporated off to give 10β-pinan-10-ol (52, 0.5 g). G.l.c. indicated 80% purity. $\delta_{CCl_4}$ = 0.70 (3H), 1.20 (3H) and 9.67 (1H).

Oxidation of 10α-pinan-10-ol:

*tert.*-Butyl chromate was made by dissolving chromium trioxide (3 g) in *tert.*-butanol (10 ml). This solution was diluted with ether (50 ml) and

10α-pinan-10-ol (1 g) added.

The mixture was allowed to react for 30 mins at room temperature, methanol (10 ml) was then added and the solution left for a further 10 min. It was then poured into a saturated sodium bicarbonate solution and extracted *via* pentane. Simple distillation under vacuum with diphenyl ether gave 10α-pinan-10-al (49; 0.75 g, containing some diphenyl ether). $\delta_{CCl_4}$ = 0.9 (3H), 1.28 (3H) and 9.53 (1H; J = 1 c.p.s.).

Rearrangement of 2,10-epoxypinanes with 'Lewis acids'

2,10-epoxypinane (0.5 g) was dissolved in solvent (100 ml). A dilute solution of 'Lewis acid' in ether was then added at 0 - 5°. Addition of a saturated solution of sodium bicarbonate followed by a separation of the layers, drying and evaporation of the solvent afforded the reaction product. The reactions resulted in the formation of 10α-pinan-10-al, 10β-pinan-10-al and polymeric material (not detected in g.l.c. analysis).

The ratio of products were determined from the NMR spectrum of the reaction product by consideration of the integrals of the signals at 9.53 and 9.67 (10α- and 10β-pinan-10-al aldehyde protons) and total

integration of the spectrum. In calculating relative amount all products were assumed to be isomeric. Results and conditions are listed in table 14.

Reduction of the epimeric pinan-10-als:

A 1:1 mixture of pinan-10-als (2 g, obtained by reaction of 2,10-epoxy-10β-pinane with boron trifluoride etherate) was added to a solution of sodium hydroxide (2 g) and sodium borohydride in methanol (200 ml) and water (10 ml) and the reaction mixture left for 2 hrs at room temperature. Work up via ether and vacuum distillation gave a mixture of alcohols (1 g), shown by g.l.c., NMR and IR to be identical to an authentic mixture of 10α-pinan-10-ol (87) and 10β-pinan-10-ol (86).

Isomerisation of 10β-pinan-10-al (52):

A 1:1 mixture of epimeric pinan-10-als which was left standing for 2 years did not exhibit a signal at 9.67 ppm (characteristic of the aldehyde proton of 10β-pinan-10-al). A g.l.c. analysis indicated two compounds in the ratio 1:1. The compounds were separated by preparative g.l.c. 5' x ¼ 15% apiezon L on celite 545, 30 - 80;

Table 14

| Lewis acid | Solvent | 2α,10-epoxy pinane | | | acid concentration ml/l | 2β,10-epoxy pinane | | |
|---|---|---|---|---|---|---|---|---|
| | | Weight recovered g. | Percentage of total aldehyde | ratio of 10α:10β aldehyde | | Weight recovered g. | aldehyde percentage of total | ratio of 10α:10β aldehyde |
| $BF_3$-$Et_2O$ | diethyl ether | 0.44 | 51% | 40:60 | 0.91 | 0.47 | 50% | 34:66 |
| " | Pentane | 0.47 | trace | 35:65 | 0.91 | - | - | - |
| " | dichloro methane | 0.49 | trace | 55:45 | 0.99 | - | - | - |
| " | Benzene | 0.49 | 20% | 50:50 | 0.476 | 0.49 | 20% | 47:53 |
| " | THF | 0.49 | 35% | 46:54 | 0.91 | 0.48 | 26% | 60:40 |
| " | Chloro form | 0.42 | 30% | 48:52 | 0.471 | 0.50 | trace | traces only |
| $H_2SO_4$ | diethyl ether | 0.45 | 13% | 21:79 | 0.91 | 0.48 | 7% | 12:88 |

temp. prog. = 5°/min., range = 100 - 200°).

Sample 1 was shown to be 10α-pinan-10-al (49; NMR spectrum identical to that of authentic sample.) Sample 2 was assigned the structure (51; p-menth-1-en-7-al) on the basis of its NMR spectrum. $\delta_{CCl_4}$ = 0.92d (6H; J = 5.5 cps), 6.14 (1H) and 9.36 (1H).

Attempted epimerisation of pinan-10-als (49 and 52):

10α-pinan-10-al (50 mg) was added to a solution of $BF_3$-etherate (1 ml/l) in ether (10 ml) and the mixture stirred at 0° for ½ hr. Isolation in the usual manner gave unreacted starting material.

Similar treatment of 10β-pinan-10-al (80%) also resulted in the recovery of starting material.

Reaction of 2,10-epoxy-10β-pinane with sulphur dioxide-pyridine:

2,10-Epoxy-10β-pinane (3 g) was added to a solution of sulphur dioxide (1.35) in pyridine (10 ml) and the reaction mixture left for 12 hrs.

Addition of water and isolation via ether gave an oil (2.90 g). The NMR spectrum indicated a complex mixture containing cyclic sulphites. A solution of sodium hydroxide (3 g) in 1:1 methanol-water (60 ml) was added to this oil and the mixture

stirred for 1 hr. A precipitate of sodium sulphite was formed. Isolation of the terpene material *via* ether gave an oil (2.0 g). Gas chromatography (5' x $\frac{1}{4}$", SE30, temp. prog. = 6°/min, range 50 - 110°) indicated five compounds with the relative peak areas; 1.4 , 4.3, 6.0, 19.8, 19.2 and 49.3 in order of elution. Compounds 3,4,5 and 6 were isolated by means of column chromatography on an alumina column, by elution with pentane-ether.

Fraction 3 (0.06 g) was identified as 10α-pinan-10-al (49) by comparison of its NMR spectrum to that of an authentic sample.

Fraction 4 (0.19 g) was pin-2-en-10-ol (NMR spectrum identical to that of authentic sample).

Fraction 5 (0.10 g) was assigned the structure (76; p-mentha-1,8-dien-7-ol) on the basis of its NMR and IR spectra. $\delta_{CCl_4}$ = 1.73 (3H), 3.92 (2H), 4.68 (2H) and 5.63 (1H). $\nu_{max}$ at 3360, 2920, 1465, 1390, 1370, 1062, 1042, 1020, 970, 918 and 894 $cm^{-1}$ (lit. cit.[112] $\nu_{max}$ at 3340, 2940, 1440, 1378, 1365, 1057, 965, 915 and 886 $cm^{-1}$).

Fraction 6 (0.79 g) was identified as a mixture of 10β-pinane-2,10-diol and 10α-pinane-2,10-diol in the ratio of 74:26, by NMR and g.l.c. The NMR spectrum of 10β-pinane-2,10-diol is identical to that of an authentic sample above. 10α-Pinane-

2,10-diol has $\delta_{CCl_4}$ = 1.09 and 1.26 ppm (by difference). Total of recovered including intermediate fractions 1.30.

Reaction of 2,10-epoxy-10α-pinane with sulphur dioxide-pyridine:

2,10-epoxy-10α-pinane (3 g) was added to a solution of sulphur-dioxide (1.35 g) in pyridine (10 ml) and left at room temperature for 12 hrs. Isolation via ether gave an oil (2.30 g). The NMR spectrum indicated a complex mixture containing pin-2-en-10-ol and a mixture of cyclic sulphites. Hydrolysis with sodium hydroxide in methanol-water was above gave an oil (1.7 g). Gas chromatography indicated five major compounds. The relative peak areas in order of elution were; 5.4, 4.0, 28.6, 6.4 and 55.6. Fractions 1 - 5 had identical retention time to fractions 2 - 6 in the previous reaction. The fractions 2 - 5 were isolated by adsorption on an alumina column and elution with pentane-ether.

Fraction 2 (0.03 g) was 10α-pinan-10-al (NMR identical to authentic sample).

Fraction 3 (0.14 g) was pin-2-en-10-ol (NMR identical to authentic sample).

Fraction 4 (0.04 g) was perrilic alcohol. (NMR identical to previous sample.)

Fraction 5 (0.5 g) was a mixture of 10β-pinane-2,10-diol and 10α-pinane-2,10-diol in the ratio of 52:48. (By comparison of the NMR spectrum with that of the previous sample.) Weight total of all fractions recovered = 0.87g.

Reduction of the monotosylates of the pinane-2,10-diols:

A mixture of pinane-2,10-diol (0.4 g; from the reaction above) was dissolved in pyridine (1 ml) and p-toluenesulphonyl chloride (0.5 g) added. The solution was left for 2 hrs at 30°. A precipitate of pyridine hydrochloride was formed. Isolation via dichloromethane gave an oil (0.57 g). This oil was added to a suspension of lithium aluminium hydride (0.5 g) in dry ether (25 ml) and heated under reflux for 2 hrs. Isolation via ether gave an oil (0.12 g).

The NMR spectrum indicated a mixture of 10α-pinan-2-ol (7) and 10β-pinan-2α-ol (8) (by comparison with the NMR spectra of authentic samples). A gas-chromatogram of the mixture (3% carbowax 20M on chromosorb-G, 100°) indicated three compounds. Two of these were identified as 10α-pinan-2-ol and 10β-pinan-2-ol. (Identical retention time to authentic sample.)

Thermal rearrangement of 10β-pinane-2,10-diol cyclic sulphite (66):

a) Cyclic sulphite (66; 0.75 g) was refluxed in pyridine (10 ml) for 2 hrs. The pyridine solution was poured into water, and extracted with pentane, (100 ml). Evaporation of solvent gave an oil (0.30 g). The infrared spectrum showed absorptions at 3400 (O-H) and 2670 and 1720 (aldehyde). G.l.c. (SE30 column) indicated pinan-10-als (not resolved by g.l.c.) and pin-2-en-10-ol (50) in the ratio of 80:20 in order of elution. The NMR spectrum was consistent with a 53:19:28 mixture of 10β-pinan-10-al (52), 10α-pinan-10-al (49) and pin-2-en-10-ol.

b) 10β-pinane-2,10-diol cyclic sulphite (1 g) was heated in carbowax 400 (5 ml) at 50 mm. Volatile products (0.45 g) distilled across. G.l.c. analysis indicated three compounds in the ratio 24:10:66, these were separated by prep. g.l.c.

Compound 1 was 1-isopropyl-4-methylbenzene (77, p-cymene). $\delta_{CCl_4}$ = 1.22d (6H; J = 6.5 cps), 2.29 (3H), 2.79q (1H, J - 7 cps) and 7.15 (4H). (lit. cit.[100] $\delta_{CDCl_3}$ = 1.22, 2.30, 2.87 and 7.08).

Compound 2 was assigned the structure α,p-dimethyl-styrene (78). $\delta_{CCl_4}$ = 2.12 (3H), 2.33 (3H), 4.98 (1H), 5.22 (1H) and 7.19q (4H). (lit. cit.[100] for α-methyl-

styrene, $\delta_{CDCl_3}$ = 2.12, 5.05, 5.36) $\nu_{max}$ at 8.28, 891, 1670, 1795 and 1909 $cm^{-1}$ (lit. cit.[113] $\nu_{max}$ 1640, 1670, 1790 and 1910 $cm^{-1}$).

Compound 3 appeared from its NMR spectrum to be a carbowax breakdown product. It was removed by extraction with water.

Thermal-sulphur dioxide rearrangement of 2,10-epoxy-10β-pinane:

2,10-Epoxy-10β-pinane (2 g) in carbowax 400 (5 ml) was heated in a stream of sulphur dioxide gas at 50 mm. An exothermic reaction took place and rearranged product (1.13 g) distilled across. G.l.c. analysis indicated three major products 18, 9 and 55% of total peak area respectively. The fractions were isolated by prep. g.l.c. and shown to be 4-isopropyl-methyl benzene (77), α,p-dimethylstyrene (78) and a carbowax breakdown product by an analogous process to that used in the previous experiment.

Thermal rearrangement of 10β-pinane-2,10-diol cyclic carbonate (70):

10β-pinane-2,10-diol cyclic carbonate (1.5 g) was dissolved in carbowax 400 (5 ml) and heated at 50 mm in a stream of nitrogen. Rearranged products (0.9 g) distilled across as an oil. G.l.c. analysis

indicated two compounds 2,10-epoxy-10β-pinane (21) and pin-2-en-10-ol (50) in order of elution (decomposition of the first eluted compound invalidated integration of the peak areas).

The NMR spectrum was consistent with a 1:2 mixture of these compounds. (By comparison with authentic spectra of compounds (21) and (50)).

Rearrangement of 2,3-epoxy-10β-pinane with zinc bromide:

2,3-epoxy-10β-pinane (19; 5 g, Light's practical grade) was dissolved in benzene 20 ml and the solution heated until refluxing. Freshly prepared zinc bromide (0.1 g, dried by heating to boiling point in a fusion tube) was then added. After refluxing for 1 hr the solution was washed with water and the solvent removed, to give 2,2,3-trimethylcyclopent-3-en-1-acetaldehyde (0.45 g). G.l.c. analysis indicated one major compound and a trace only of one other compound. $\delta_{CCl_4}$ = 0.78 (3H), 1.00 (3H), 1.63 (3H), 5.22 (1H) and 9.75 (1H). (lit. cit.[79] $\delta_{CCl_4}$ = 0.90 (3H), 1.00 (3H), 1.63 (3H), 5.22 (1H) and 9.75 (1H)).

10α-pinan-3-one did not react with zinc bromide under these conditions. (Recovered starting material identified by its NMR spectrum.)

Thermal rearrangement of cyclic sulphites from 10β-pinan-2,3α-diol (68 and 69):

a) Cyclic sulphite (1:1 mixture of 68 and 69; 2 g) was dissolved in carbowax 200 (5 ml) and heated at 50 mm pressure. The volatile products were distilled over in a stream of nitrogen. Ether (50 ml) was added to the distillate and the ether solution washed with saturated sodium bicarbonate solution (2 x 50 ml). Evaporation of the solvent gave an oil (1.1 g).

G.l.c. analysis indicated two compounds in the ratio of 96:4. The major compound was identified as 10α-pin-3-one (pinocamphone) $\delta_{CDCl_3}$ = 0.89 (3H) 1.09d (3H; J = 7 cps) and 1.33 (3H). $\delta_{CCl_4}$ = 0.90, 1.04 and 1.22. $\nu_{max}$ at 1709 $cm^{-1}$ (lit. cit.[83] $\delta_{CDCl_3}$ = 0.88, 1.09d (J = 7 cps) and 1.32).

The minor compound was identified as 2,2,3-trimethyl-cyclopent-3-ene-1-acetaldehyde (by identical retention time to an authentic sample).

b) Reaction under the same condition as above using an atmosphere of sulphur dioxide instead of nitrogen gave the same result.

c) Reaction as (a) above on half quantity of cyclic sulphite and addition of potassium cyanide gave an oil (0.5 g) on work up.

G.l.c. analysis indicated four compounds. Compound 1 (trace only) was identified as 2,3-epoxy-10β-pinane (from its retention time compared to a commercial sample). Compounds 2 and 4 (minor products) were partially obscured by compound 3 (major product) which was identified as 10α-pin-3-one (by g.l.c. retention).

d) On refluxing the cyclic sulphite in pyridine for 2 hrs followed by isolation *via* ether, unchanged starting material was recovered.

Thermal rearrangement of 2,3-epoxy-10β-pinane (19):

a) 2,3-epoxy-10β-pinane (2 g) was heated with potassium cyanide (0.5 g) in carbowax 400 at 50 mm. The product was distilled across in a stream of nitrogen to give an oil (1.0 g) shown by g.l.c. and NMR to be unchanged starting material.

b) 2,3-epoxy-10β-pinane (2 g) was heated in carbowax 400 (5 ml) at 50 mm while sulphur dioxide was passed through the solution. An exothermic reaction took place and the rearranged product distilled out to give an oil (1.8 g). G.l.c. analysis indicated five fractions. The relative percentage in order of elution was; 10, 11, 22, 55 and 2%.

The five fractions were isolated by preparative

g.l.c. on a 20% carbowax 20M column.

Compound 1 was assigned the structure (80), 1-isopropylidine-4-methyl-cyclohexa-2,4-diene.

$\delta_{CCl_4}$ = 1.74 (6H), 4.75 (2H), 5.42 (1H), 5.74 (2H) and methylene region (3H); $UV_{max}$ at 265 mμ (lit. cit[114] for phellandrene (81) $UV_{max}$ at 263 m ). On standing the hydrocarbon isomerised to compound 2.

Compound 2 was identified as 4-isopropyl-methyl benzene (77; p-cymene) $\delta_{CCl_4}$ = 1.22d (6H, J = 6.5 cps), 2.29 (3H), 2.79q (1H, J = 7 cps) and 7.15 (4H) (lit. cit.[100] $\delta_{CDCl_3}$ = 1.22, 2.30, 2.87 and 7.08).

Fraction 3 was shown to contain two compounds by NMR, an aldehyde and an aromatic hydrocarbon. The aldehyde was removed as its bisulphite complex and the pure hydrocarbon isolated. This was shown to be α,p-dimethylstyrene (78). $\delta_{CCl_4}$ = 2.12 (3H), 2.33 (3H), 4.98 (1H), 5.22 (1H) and an A.B. quartet centre 7.19 (4H); (lit. cit. for α-methyl styrene[100] J = 2.12, 5.05, 5.36). $\nu_{max}$ at 828, 891, 1670, 1795 and 1909 $cm^{-1}$ (lit. cit. $\nu_{max}$ at 1640, 1670, 1790 and 1910 $cm^{-1}$). The aldehyde was deduced to be 2,2,4-trimethyl cyclopent-3-ene-1-acetaldehyde (79) from its NMR spectrum and its retention time relative to compound 4. $\delta_{CCl_4}$ = 0.82 (3H), 1.08 (3H), 1.65 (3H), 5.10 (1H) and 9.73 (1H).

From the g.l.c. and NMR data above the relative percentage of the two compounds (78) and (79) are 7 and 15% respectively.

Compound 4 was identified as 2,2,3-trimethylcyclopent-3-ene-1-acetaldehyde from its NMR spectrum. $\delta_{CCl_4}$ = 0.78 (3H), 1.00 (3H), 1.65 (3H), 5.26 (1H) and 9.73 (1H). (lit. cit.[79] = 0.90 (3H)*, 1.00 (3H), 1.63 (3H), 5.22 (1H) and 9.75 (1H).)

Fraction 5 was identified as 10α-pin-3-one. (NMR and IR spectra were identical to those of the previously quoted sample.

* The NMR spectrum obtained was identical to that of a sample prepared by the literature[79] method. The value of 0.90 quoted by Lewis and Hedrick[79] must be erroneous.

Thermal rearrangement of 10β-pinane-2,3α-diol cyclic carbonate (70):

a) Cyclic carbonate (70; 0.5 g) was dissolved in carbowax 400 (5 ml) and heated at 50 mm. Unchanged carbonate distilled across (by NMR).

b) Cyclic carbonate (1.5 g) was dissolved together with potassium cyanide (0.5 ) in carbowax 400 (5 ml) and heated at 50 mm. The rearranged products (1.04 g) distilled across in a stream of nitrogen at

ca. 200°. G.l.c. analysis indicated three compounds in the ratio 5:42.5:52.5 in order of elution. Compound 1 was identified as 10α-pinan-3-one (48; identical retention time with an authentic sample).

Compounds 2 and 3 were isolated by preparative g.l.c. (on a 5' x ¼" 20% carbowax on celite 545 30-80 aluminium column).

Compound 2 was identified as 10β-pin-3-en-2-ol (71) $\delta_{CCl_4}$ = 0.97 (3H), 1.25 (3H) and 1.37(3H) $\delta_{CDCl_3}$ = 0.97 (3H), 1.32 (3H), 1.37 (3H), 5.50 m. (1H) and 6.27 m (1H). (lit. cit.[83] $\delta_{CDCl_3}$ = 0.95, 1.32, 1.37, 5.44 and 6.29.)

Compound 3 was identified as pin-2(10)-en-3α-ol by its NMR and IR spectra (these were identical to those previously quoted).

Acid rearrangement of 2,10-epoxy-10β-pinan-3α-ol (72):

2,10-epoxy-10β-pinan-3α-ol (0.50 g) was added to a solution of p-toluene-sulphonic acid (0.13 g) in methanol (70 ml) and the mixture refluxed for 1 hr. A saturated solution of sodium bicarbonate in water (20 ml) was then added and the methanol evaporated off. Isolation via dichloromethane gave an oil (0.48 g).

The NMR spectrum indicated a mixture of methyl

ethers. Thin layer chromatography on alumina indicated two major compounds. These were separated by adsorption onto an alumina column and elution with ether-pentane.

The first major fraction (0.115 g) had an NMR spectrum which was not consistent with a pure monomer. Mass spectral data indicated a mixture. Moderately intense peaks at 302 and 567 suggest dimerisation and trimerisation.

The second major fraction (0.120 g) had an NMR spectrum which was consistent with pure 2endo-methoxy-fenchane-6exo,10-diol. $\delta_{CCl_4}$ = 0.91 (3H), 1.09 (3H), 1.43 (2H, multiplet), 1.73d (2H, J = 4 cps), 2.34 (1H octet J' = 13 cps, J' = 7 cps, J'' = 3 cps), 2.97 (2H; Oh, removed by addition of $D_2O$), 3.10 (1H), 3.34 (3H), 3.90 (2H) and c. 4.33 (1H , quartet J = 7 cps, J' = 3 cps). On irradiating 117 cps upfield the quartet c 4.33 collapsed to a doublet J = 7 cps. $\nu_{max}$ at 2940 $cm^{-1}$ (O-H stretch).

Acid rearrangement of 2,10-epoxy-10β-pinan-3β-ol (73):

210-epoxy-10 β-pinan-3β-ol (1.0 g) was added to a solution of p-toluene sulphonic acid (0.26 g) in methanol (140 ml) and the mixture refluxed for 1 hr. A saturated solution of sodium bicarbonate in water

(40 ml) was then added and the methanol evaporated off. Work up via dichloromethane gave an oil (1.05 g).

Thin layer chromatography on alumina indicated three major and four minor fractions. The major fractions were separated by column chromatography. The NMR spectra were not consistent with pure monomeric compound. No pinocarvone (20) was detected.

Reaction of β-pinene with mercuric acetate:

Mercuric acetate (31.9 g) was dissolved in water (100 ml) and tetrahydrofuran (100 ml) added. The solution was stirred vigorously and β-pinene (13.6 g; Fluka pract. grade) was added. A rapid colourchange (from yellow to colourless) was observed. After 10 mins sodium hydroxide solution (100 ml, 3M aq.) was added followed by sodium borohydride (100 ml; 0.5M in sodium hydroxide 3M). Addition of salt allowed separation of layers. Removal of solvent from the organic layer gave an oil (13.0 g). G.l.c. analysis indicated α- and β- pinene and major compound in order of elution.

The major compound was isolated by fractional distillation to give an oil (5.3 g), $b.p._{1}$ = 125 - 130°. MW determination by Rast's method (m.p. depression of camphor) gave MW = 260. MW determination by

means of an osmometer gave MW = 248. (Found: C, 88.9; H, 11.3. $C_{20}H_{30}$ requires: C, 88.9; H, 11.1). An IR spectrum showed no absorption at ca. 3000 $cm^{-1}$ (no O-H). The NMR spectrum ($\delta_{CCl_4}$ = 0.83, 1.27 and 4.63 (3) and 5.17 (4) ) indicated a mixture of compounds. A mass spectrum showed the compounds to have a molecular weight of 270.

Alkaline rearrangement of 2,10-epoxy-10β-pinan-3α-ol (72):

2,10-epoxy-10β-pinan-3α-ol (0.25 g) was refluxed with a solution of sodium hydroxide (1 g) in methanol (10 ml) and water (5 ml) for 2 hrs.

The methanol was evaporated off and the product isolated *via* pentane to give an oil (0.20 g). The NMR spectrum was consistent with a 1:1 mixture of pinocarvone (20) and starting material. $\nu_{max}$ at 1720 and 1633 $cm^{-1}$ (lit. cit.[83] for pinocarvone 1709 and 1626). G.l.c. analysis (on polar and non-polar columns) confirmed the presence of the ketone.

Alkaline rearrangement of 2,10-epoxy-10β-pinan-3β-ol:

2,10-epoxy-10β-pinan-3β-ol (0.50 g) was refluxed with a solution of sodium hydroxide (2 g) in methanol (20 ml) and water (10 ml) for 2 hrs.

Evaporation of the methanol and isolation of product via pentane gave an oil (0.31 g). Shown by g.l.c., NMR and IR to be essentially pinocarvone.

## RATE DETERMINATIONS

The rates of formation of pinocarvone (23) from the reaction of the 2,10-epoxy-10β-pinan-3-ols (72 and 73) with sodium hydroxide in 1:10 methanol water were studied. The reaction mixtures were maintained at 60° in a thermostat bath. Aliquots of reaction mixture were withdrawn at regular intervals and the optical density at 252 mμ determined using a Beckman DB-G spectrophotometer.

Results:- The results obtained are listed in tables 14 and 15. The optical density (O.D.) was plotted against time (t min). From the best lines, intercepts at t and Δt were obtained. The values

Table 14

2,10-Epoxy-10β-pinan-3α-ol (conc. 0.0549 g/l)

| $[OH^-]$ = 0.50 | | $[OH^-]$ = 0.25 | | $[OH^-]$ = 0.125 | |
|---|---|---|---|---|---|
| t min. | O.D. | t min. | O.D. | t min. | |
| 10 | 0.164 | 11 | 0.120 | 14 | 0.074 |
| 20 | 0.220 | 22 | 0.141 | 26 | 0.088 |
| 31 | 0.279 | 32 | 0.182 | 36 | 0.120 |
| 54 | 0.432 | 56 | 0.278 | 62 | 0.170 |
| 75 | 0.520 | 77 | 0.340 | 79 | 0.203 |
| 109 | 0.622 | 113 | 0.454 | 131 | 0.288 |
| 159 | 0.760 | 162 | 0.565 | 167 | 0.350 |
| 194 | 0.821 | 196 | 0.625 | 217 | 0.424 |
| 242 | 0.870 | 246 | 0.700 | 252 | 0.465 |
| | | | | 443 | 0.830 |

Table 15

2,10-Epoxy-10β-pinan-3β-ol (conc. = 0.0402 g/l)

| $[OH^-] = 0.5$ | | $[OH^-] = 0.25$ | | $[OH^-] = 0.125$ | | $[OH^-] = 0.0625$ | |
|---|---|---|---|---|---|---|---|
| t min. | O.D. | t min. | O.D. | t min. | O.D. | t min. | O.D. |
| 10 | 0.382 | 11 | 0.272 | 12 | 0.219 | 13 | 0.191 |
| 14 | 0.410 | 18 | 0.348 | 19 | 0.290 | 20 | 0.238 |
| 21 | 0.500 | 24 | 0.413 | 27 | 0.370 | 28 | 0.270 |
| 29 | 0.560 | 36 | 0.478 | 39 | 0.384 | 40 | 0.287 |
| 42 | 0.590 | 53 | 0.535 | 54 | 0.430 | 55 | 0.325 |
| 56 | 0.610 | 61 | 0.563 | 67 | 0.458 | 68 | 0.360 |
| 69 | 0.610 | 89 | 0.590 | 90 | 0.515 | 91 | 0.415 |
| 98 | 0.610 | 111 | 0.600 | 113 | 0.525 | 114 | 0.458 |
| | | 135 | 0.610 | 136 | 0.560 | 137 | 0.500 |
| | | 155 | 0.610 | 156 | 0.575 | 157 | 0.515 |

for $\log(D_{t+\Delta t} - D_t)$ (where $D_t$ is optical density at time t) are shown in tables 16 and 17.

Table 16

2,10-Epoxy-10β-pinan-3α-ol $\Delta t$ = 120 min.

| t min. | $\log(D_{t+\Delta t} - D_t)$ | | |
|---|---|---|---|
| | $[OH^-] = 0.50$ | $[OH^-] = 0.25$ | $[OH^-] = 0.125$ |
| 20 | - 0.301 | - 0.416 | - 0.638 |
| 40 | - 0.377 | - 0.455 | - 0.659 |
| 60 | - 0.469 | - 0.517 | - 0.678 |
| 80 | - 0.538 | - 0.568 | - 0.700 |
| 100 | - 0.638 | - 0.603 | - 0.732 |

Table 17

2,10-Epoxy-10β-pinan-3β-ol

| t min | $[OH^-]$= 0.5 t = 15min | $[OH^-]$= 0.25 t = 20 min | $[OH^-]$= 0.125 t = 40 min | $[OH^-]$= 0.0625 t = 50 min |
|---|---|---|---|---|
| 10 | | - 0.710 | | |
| 15 | - 0.850 | | | |
| 20 | - 1.03 | - 0.902 | - 0.802 | - 0.825 |
| 25 | - 1.21 | | | |
| 30 | - 1.40 | - 1.08 | - 0.895 | - 0.857 |
| 35 | - 1.60 | | | |
| 40 | | - 1.23 | - 1.00 | - 0.893 |
| 50 | | - 1.37 | - 1.09 | - 0.924 |
| 60 | | - 1.53 | - 1.16 | - 0.955 |
| 70 | | - 1.72 | - 1.22 | - 0.972 |

From a plot of $\log(D_{\Delta t+t}-D_t)$ versus t the pseudo first order rate constants ($k_1$) are determined. The values of $k_1$ are listed in table 18.

The second order rate constants ($k_2$) were determined from a plot of $k_1$ versus $[OH^-]$.

For 2,10-epoxy-10β-pinan-3α-ol

$$k_2 = 3.0 \times 10^{-4}\ l.mole^{-1}\ sec^{-1}$$

For 2,10-epoxy-10β-pinan-3β-ol

$$k_2 = 33 \times 10^{-4}\ l.mole^{-1}\ sec^{-1}$$

Table 18

| $[OH^-]$ moles.$l^-$ | $k_1 \times 10^4$ $sec^{-1}$ | |
|---|---|---|
| | Epoxide (72) | Epoxide (73) |
| 0.0625 | | 1.2 |
| 0.125 | 0.57 | 3.6 |
| 0.250 | 0.97 | 6.5 |
| 0.500 | 1.7 | 15.2 |

A typical run (0.5M NaOH, epoxide (72)) is illustrated by the graphs in fig. 33 and 34. Plots of $k_1$ versus $[OH^-]$ are shown in fig. 35 and 36.

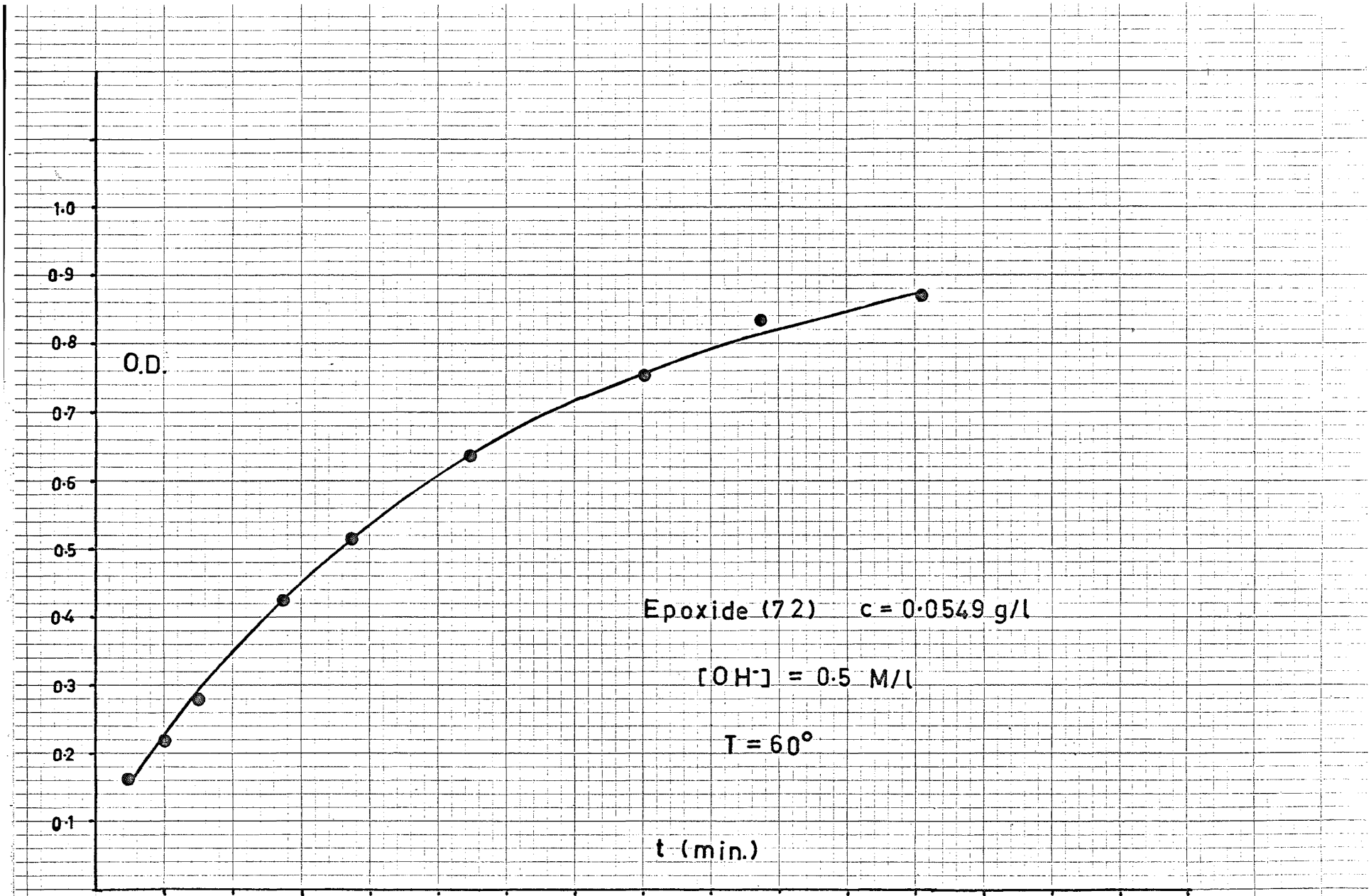
O.D.
1·0
0·9
0·8
0·7
0·6
0·5
0·4
0·3
0·2
0·1
20
40
60
80
100
120
140
160
180
200
220
240
260
Epoxide (72) c = 0·0549 g/l
[OH⁻] = 0·5 M/l
T = 60°
t (min.)

Fig. 33

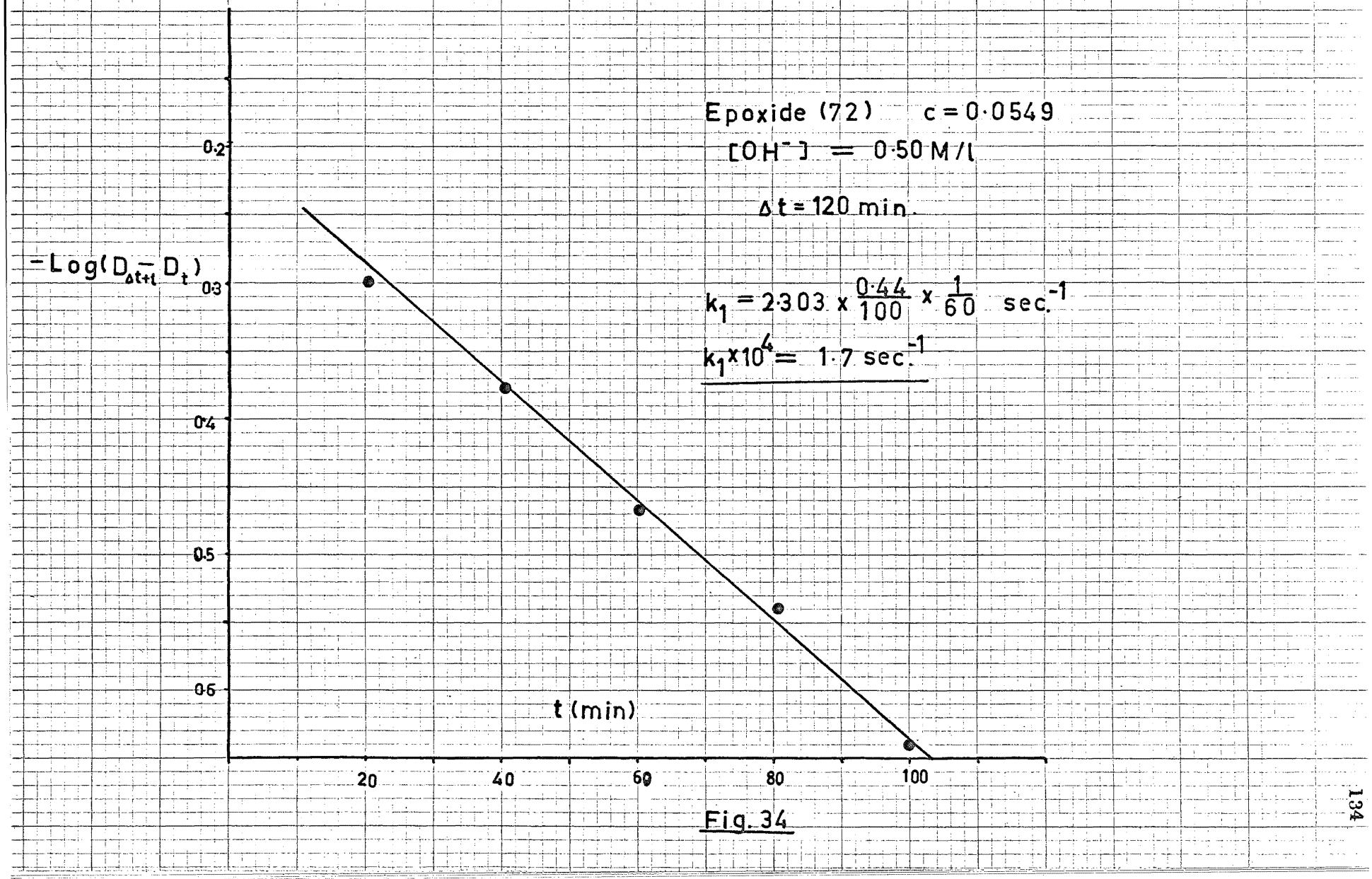
Epoxide (72) c = 0·0549
[OH⁻] = 0·50 M/l
Δt = 120 min.
$k_1 = 2{\cdot}303 \times \frac{0{\cdot}44}{100} \times \frac{1}{60}$ sec.⁻¹
$k_1 \times 10^4 = 1{\cdot}7$ sec.⁻¹
$-\mathrm{Log}(D_{\Delta t+t} - D_t)$
0·2
0·3
0·4
0·5
0·6
t (min)
20
40
60
80
100

Fig. 34

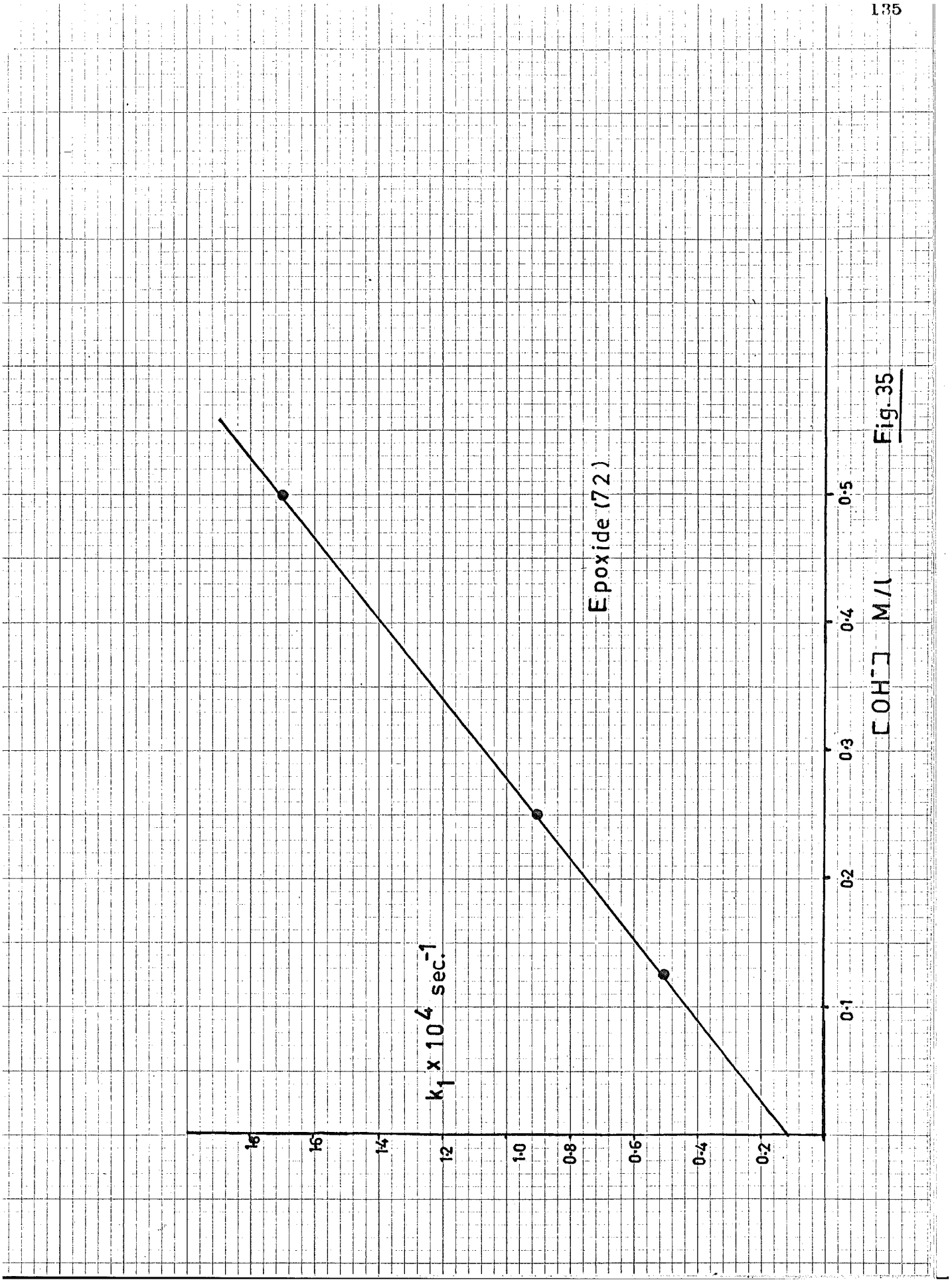
Epoxide (72)
$k_1 \times 10^4$ sec.$^{-1}$
[OH$^-$] M/l
0·2
0·4
0·6
0·8
1·0
1·2
1·4
1·6
0·1
0·2
0·3
0·4
0·5

Fig-35

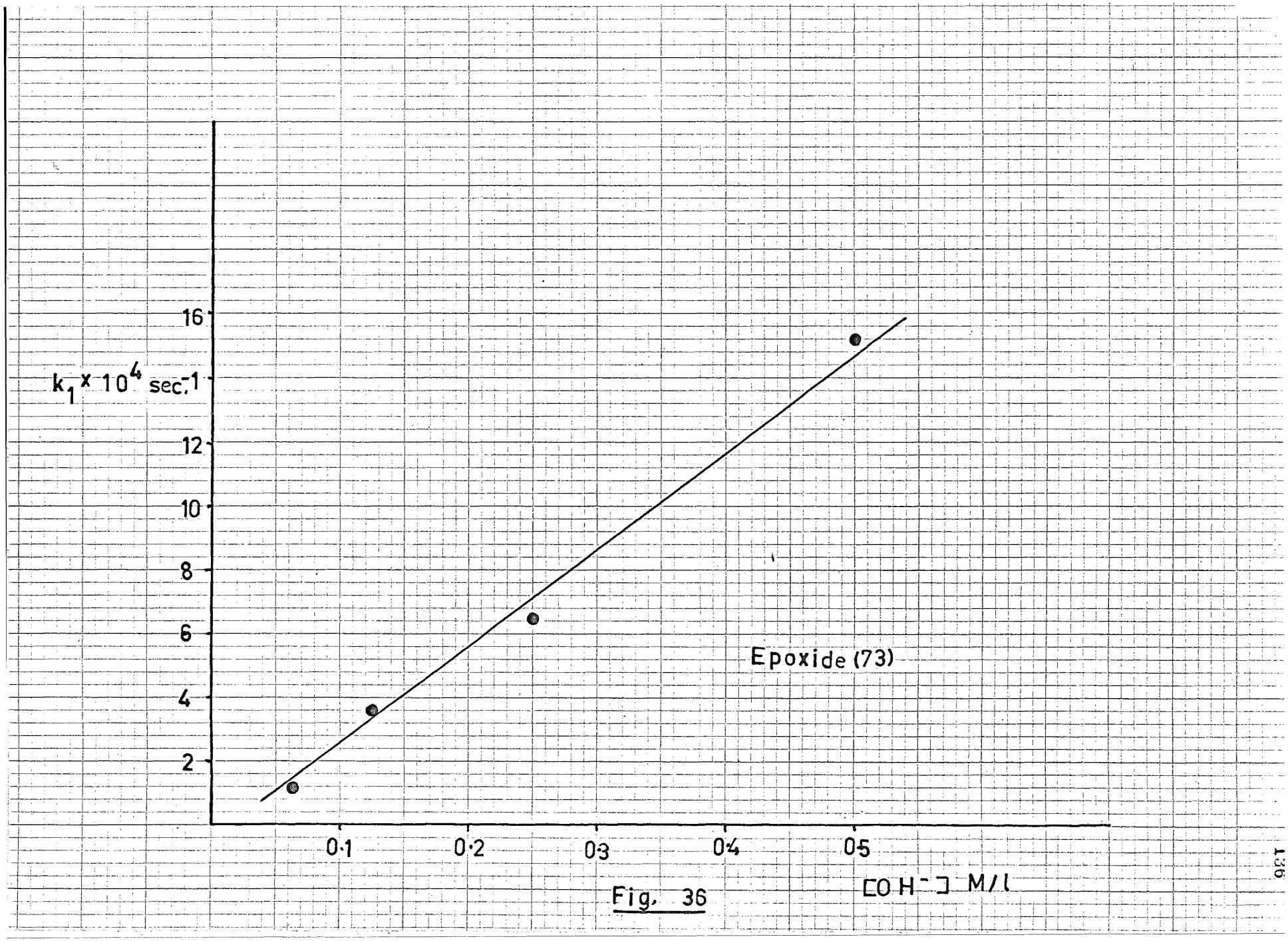


Fig. 36

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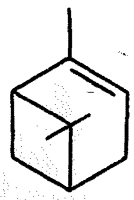

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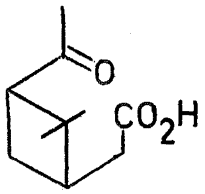


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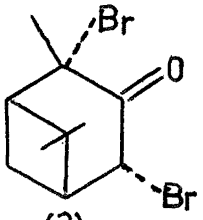


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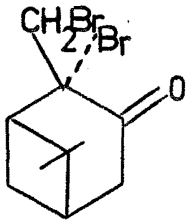


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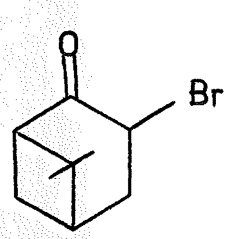


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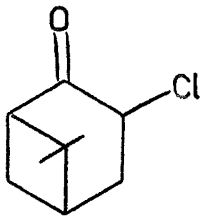


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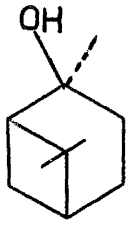


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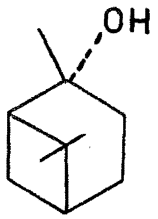


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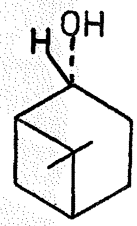


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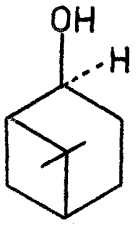


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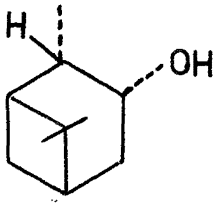


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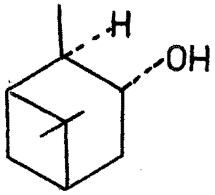


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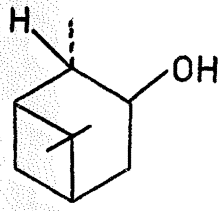


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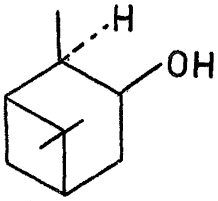


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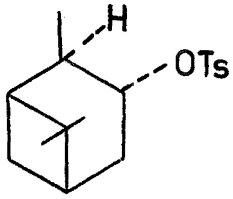


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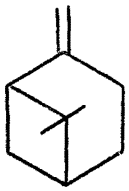

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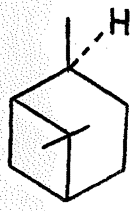


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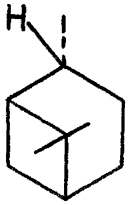


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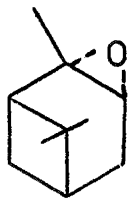


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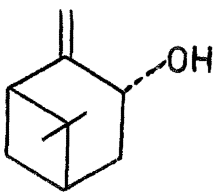


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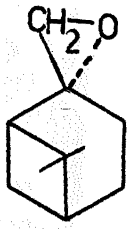

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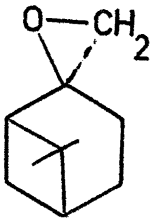

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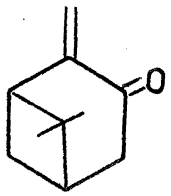

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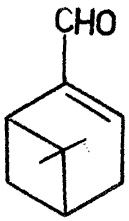

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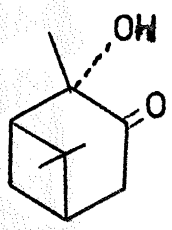

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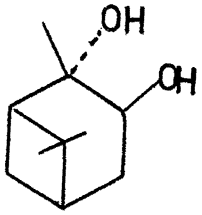

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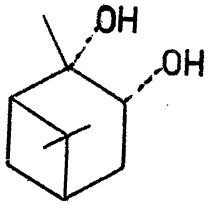

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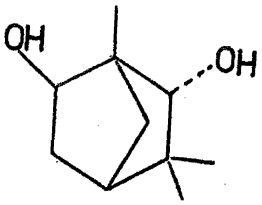

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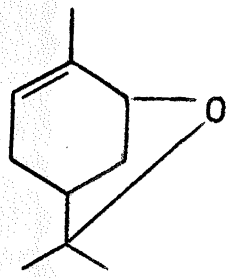

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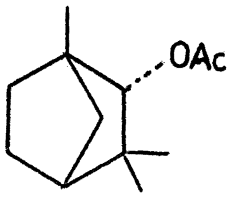

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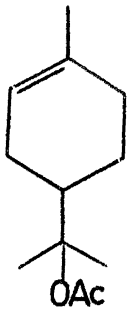

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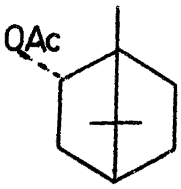

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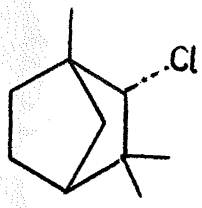

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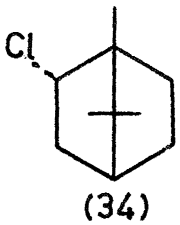

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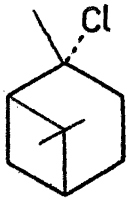

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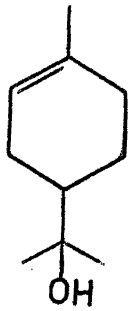

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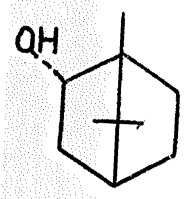

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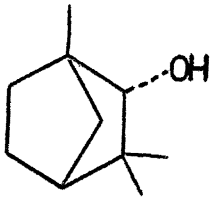

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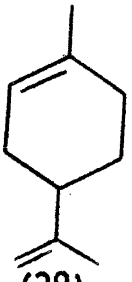
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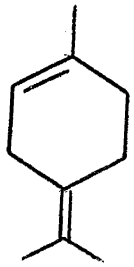
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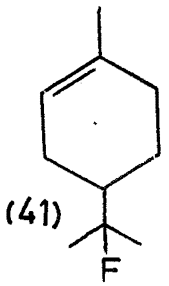


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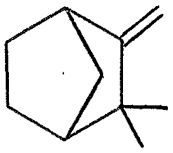

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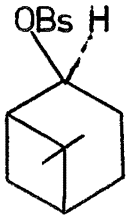


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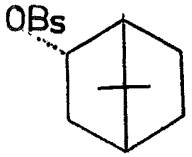


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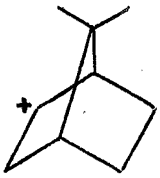

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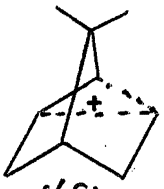

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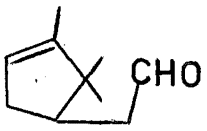


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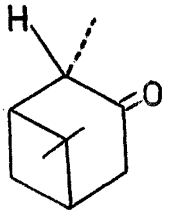


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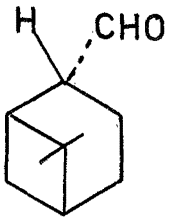


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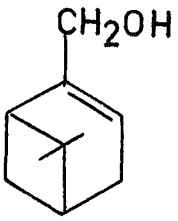


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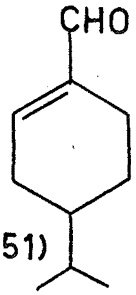


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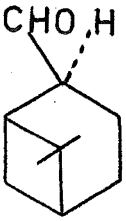


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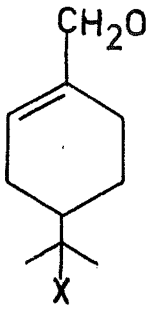
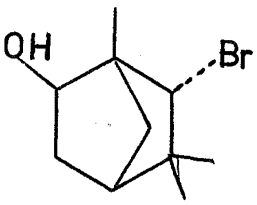
(53)

a) X = OAc

b) X = OCHO

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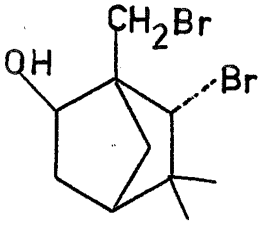


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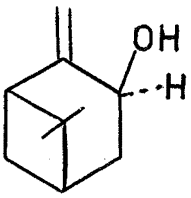


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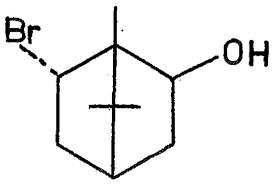


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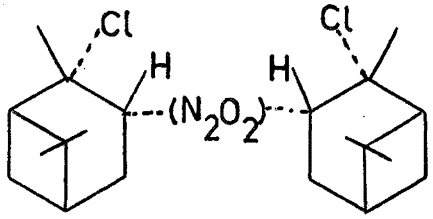


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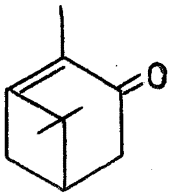


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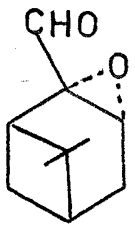


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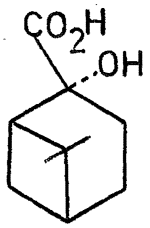


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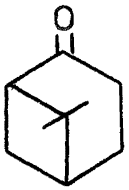


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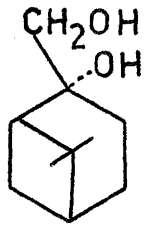


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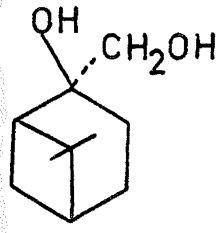


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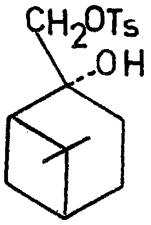


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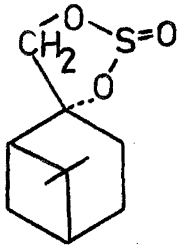


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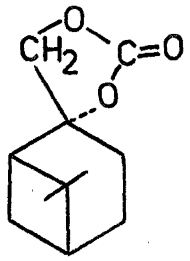


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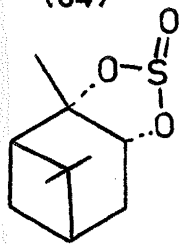


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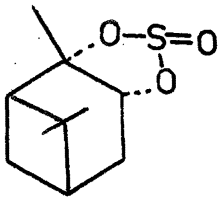


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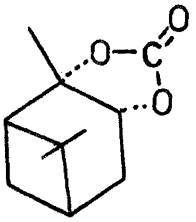


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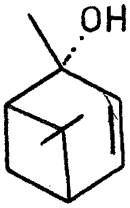


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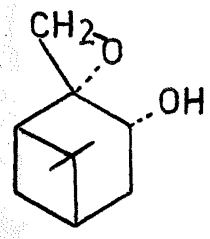


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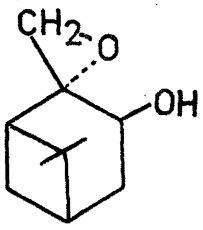


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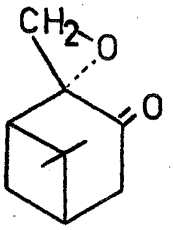


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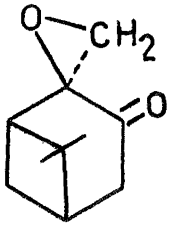


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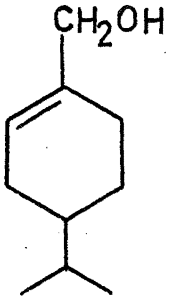


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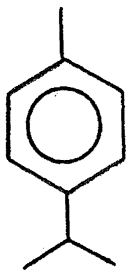

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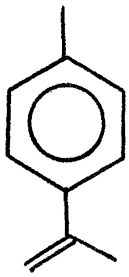

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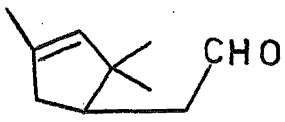


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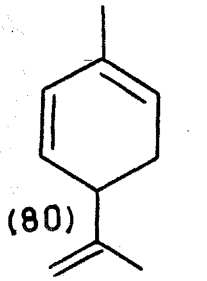

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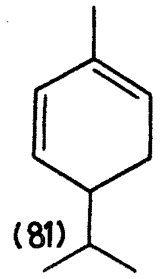

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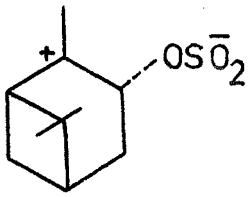

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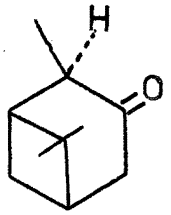

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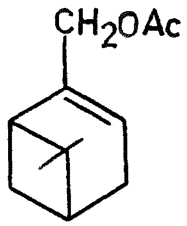

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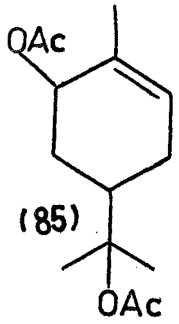

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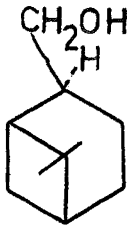

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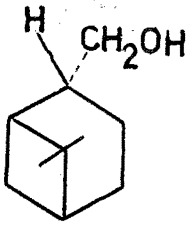

(87)